



THE PHARMACOLOGY  
OF ANESTHETIC DRUGS





*Fourth Edition*

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

A SYLLABUS FOR STUDENTS AND CLINICIANS

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To

E A ROVENSTINE M.D

*who with his emphasis upon the basic sciences  
in the teaching of anesthesiology  
prompted the preparation  
of this syllabus*





## PREFACE TO THE FOURTH EDITION

Since World War II chemists and pharmacologists have intensified their interest in the relationship of chemical structure of drugs to pharmacologic activity. This has led to the synthesis, laboratory investigation and clinical trial of numerous new compounds. Families of drugs having similar pharmacological responses have been developed from single parent derivatives by varying side chains and chemical groupings. As a result, anesthesiologists have been besieged with numerous depressants, stimulants, antagonists and adjunctive drugs. Many of these have enjoyed only a brief span of existence and have already been discarded or supplanted by apparently more effective substitutes. Others appear to have earned a more permanent position and are enjoying widespread use.

In addition to research on new products during the past decade, the older conventional drugs have been studied in more detail with more precise methods and refined apparatus. In many cases data heretofore available only from animal studies have been obtained in man. In this edition, therefore, it was necessary to both add data on new drugs and to bring up-to-date material on the well-established drugs used in clinical anesthesiology. As heretofore, the emphasis has been placed upon the anesthesiologist's use and interest in these compounds.

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*New Orleans, Louisiana*





## PREFACE TO THIRD EDITION

NEARLY A DECADE has passed since the first edition of this book was prepared. During this period anesthesiology has grown into a well-defined medical specialty. At the time of preparation of the original text knowledge of certain aspects of anesthesiology was meagre.

Although much still remains to be learned concerning basic principles and fundamentals considerable data has been added to our fund of knowledge over the ten year period. These advances in our knowledge have been in all aspects of anesthesiology. The greatest advances, however have been in the pharmacological aspects of the science. Most of the recently acquired pharmacological data has been obtained in the operating room on surgical patients. Information not available from patients has been supplied by the laboratory. This newer clinical experience, coupled with the recently added laboratory investigations have made possible a re-evaluation of earlier reported subject matter. In many instances modification of the existing subject matter has been necessary in others the previous observations are still acceptable. As a result, certain gaps have appeared in the text which need to be filled if the book is to continue to serve the purposes for which it was intended and which it seems to have filled, as evidenced by five printings of the second edition. The author feels that before any further publication is made the original text should be completely rewritten and brought as nearly up-to-date as possible.

The purpose and general plan remains the same. Likewise, there has been no departure from the original form save for the inclusion of tables of the less common drugs used only occasionally by the anesthesiologist. Some of the more pertinent subjects of clinical importance have been elaborated upon and presented in greater detail. This has resulted in a larger volume. The properties and actions of non narcotic drugs used in conjunction with anesthesia such as curare, the central nervous system stimulants, and drugs acting upon the autonomic nervous system have also been summarized. In describing these substances emphasis has been placed on their relationship to anesthesiology.

The writer is indebted to Mr. William Branks Stewart of the Department of Visual Education Louisiana State University School of Medicine for the preparation of the diagrams used throughout the text.

*New Orleans Louisiana*

JOHN ADRIANI M.D.



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THE PHARMACOLOGY  
OF ANESTHETIC DRUGS





$$\begin{array}{c} \text{H} \\ | \\ \text{CH}_3 - \text{C} - \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$$

CTI  
100-611-1111



Cytoplasm



CH  
Int-Pratman



**Answer**



100

**ALCOHOLS**—Containing one hydroxyl group are known as monohydric alcohols, two dihydric, three trihydric, and so forth. Alcohols containing alphabetic or monocyclic aliphatic groups are important in local anesthetics (see local anesthetics). Alcohol solubility depends upon the position of the hydroxyl group.

[illegible]

**Primary Alcohols**—Primary alcohols have two hydrogens atoms on the hydroxyl bearing carbon. Ethyl alcohol is the most important primary aliphatic alcohol with anesthetic activity.



Secondary Alcohols—Secondary alcohols have one hydrogen and two radicals on the hydroxyl bearing carbon.  
The important secondary aliphatic alcohol is used for anesthesia or hypnosis



**Tertiary Alcohols**—Tertiary alcohols have three radicals on the hydroxyl bearing atom. *Amiprin hydrate* is the only currently employed drug in this group.

[illegible]

**ALDEHYDES**—Oxidation of primary alcohols of a hydrogen atom of an aldehyde and polymerize to form metaldehydes and paraldehydes. Paraldehydes and acetals depress important aliphatic compounds.

**Aliphatic Aldehydes**—A important aliphatic compounds are nervous system depressants Acetaldehyde is the least toxic of the group, but is irritating and feeble in its action. **Heterocyclic Aldehydes**—No important aromatic and heterocyclic aldehydes exist in these groups.

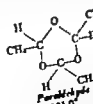
**Paraldehyde**—Higher molecular weight paralkdehydes have been studied but are toxic. Paraldehyde the simplest member of the series, is useful as a sedative and hypnotic. Paraldehyde is derived from acetaldehyde.

Formaldehyde  
NF - 21.5"

*Acetabularia*



Two planned releases



Parachute

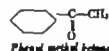
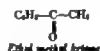
The conversion of an alcohol into an aldehyde causes an increase in irritating properties and a weakening of narcotic potency (ethyl alcohol is more useful and less irritating than acetaldehyde its corresponding aldehyde) Potency increases as molecular weight increases. Water solubility and volatility decrease as molecular weight increases.

Polymers of aldehydes form an entirely new series of compounds distinctly unlike aldehydes. Paraldehydes are more potent than the aldehydes from which they are derived. They are also less soluble, less volatile and less irritating. Potency and toxicity increase as molecular weight increases. Volatility decreases as molecular weight increases. Halogenation of aldehydes enhances their potency (see halogenated derivatives)

**ACETALS**—The interaction of alcohols with aldehydes produces acetals. Acetal is the most useful member of this group

**KETONES**—Oxidation of secondary alcohols yields ketones—compounds containing the carbonyl ( $C=O$ ) group. Ketones are of relatively little importance as central nervous system depressants. Halogenated ketones unlike the aldehydes are not useful as nervous system depressants.

Phenyl methyl ketone or *acetophenone* has been used as a hypnotic and sedative. Potency of ketones increases as molecular weight increases.



**ACIDS**—Organic acids are compounds containing the carboxyl ( $\text{COOH}$ ) group. The replacement of a hydrogen atom of a hydrocarbon by a carboxyl group nullifies its action as a nervous system depressant. The carboxylic acids therefore are of no importance as anesthetic agents.

**ESTERS**—The interaction of an organic acid with an alcohol results in an ester. Esters may be derived from aliphatic, alicyclic, aromatic and heterocyclic acids and alcohols. Esters derived from aliphatic alcohols and carboxylic acids are mild hypnotic and sedative substances. None are clinically important. Such esters are less potent than the alcohols from which they are derived. The majority of local anesthetic drugs are complex esters of aromatic or heterocyclic acids and complex alcohols (see local anesthetic drugs)

**ETHERS**—Compounds formed by attaching two organic radicals to an oxygen atom are known as ethers. They may also be termed organic oxides. Ethers may be classed as aliphatic, alicyclic, aromatic or heterocyclic. Aliphatic and alicyclic ethers are potent and useful for general anesthesia. Aromatic and heterocyclic ethers play no role in general anesthesia but appear in local anesthetics. Ethers may be symmetrical if both radicals attached to the oxygen atom are similar or unsymmetrical if they are dissimilar. Unsaturated linkages may appear on one or both radicals of ethers.

**Saturated Aliphatic Ethers**—Diethyl ether is the most useful and potent of this group. Ethyl propyl ether has been used clinically also but is not generally accepted. Diisobutyl ether has been used clinically but is not satisfactory.



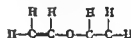
**Unsaturated Aliphatic Ethers**—Diisopropyl ether is the most important compound of this group. Higher molecular weight compounds are not satisfactory.



**Mixed Ethers**—Various alicyclic and aliphatic ethers have been prepared and tried clinically. None has yet attained any widespread clinical use. Cyclopropyl methyl ether or cyclopropane, cyclopropyl ethyl ether or cyclopropane have been tried, but discarded.



Diisopropyl ether  
BP  $-35.6^\circ$



Ethyl isopropyl ether

Aliphatic and alicyclic ethers are more volatile than the alcohols to which they are related or from which they are derived. They are miscible with lipoids and hydrocarbons, highly flammable and slightly soluble in water. The presence of unsaturated linkages and the presence of the alicyclic radicals increases their potency.

Low molecular weight ethers are very volatile, irritating and require low concentrations for surgical anesthesia. Toxicity increases with increase in molecular weight. Halogenated ethers are not generally useful. Unsaturation causes an increase in secretory activity of ethers.

**HALOGENATED DERIVATIVES**—Compounds derived from chlorine, fluorine and bromine are useful central nervous system depressants. Iodine yields toxic or non-anesthetic derivatives. The most useful compounds are aliphatic hydrocarbons, alcohols, and aldehydes. Alkyl compounds are of no importance. Aromatic derivatives are toxic following aliphatic halogenated compounds are important.

**Halogenated Hydrocarbons (narcotics)**—Many derivatives of bromine and chlorine have been prepared which possess a depressant action on the nervous system. Chloroform, *fluothane* and *ethyl chloride* are currently used. The majority of derivatives in this group are administered by inhalation.

**Halogenated Hydrocarbons (non-narcotics)**—Trichloroethyl ether is the only member of this group employed clinically for inhalation, other derivatives are irritating, toxic or not easily volatilized.

**Halogenated Alcohols**—Trichloroethyl alcohol and tribromoethyl alcohol are potent hypnotics used for basal anesthesia. Drugs in this group are non-volatile and cannot be administered by inhalation. They are formed by reduction of aldehydes. Halogenation increases the potency of aliphatic alcohols.

**Halogenated Aldehydes**—Chloral and bromal are used clinically. These derivatives are more volatile than the corresponding halogenated alcohols. Halogenation diminishes irritating qualities and improves the potency of aliphatic aldehydes. Hydrates form when they interact with water. Halogenated aldehydes, like the alcohols, are not sufficiently volatile to be used for inhalation.

Halogenation enhances narcotic potency and causes a decrease in volatility of aliphatic substances. Inflammability decreases as the number of halogen atoms increases. Chlorinated hydrocarbons are of limited usefulness because they are potent than brominated compounds. Many halogenated hydrocarbons are of little clinical importance with the exception of toxic to the heart and liver.

**SULPHONATED COMPOUNDS**—Sulphur containing compounds are of little clinical importance with the exception of the thio-barbiturates (see barbiturates) and the sulphonated aliphatic compounds derived from sulphonic acid. The sulphone methanes, derived from ethyl sulphonic acid, possess hypnotic properties. Aromatic sulphonic acid derivatives do not.

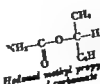
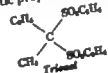
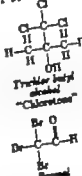
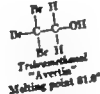
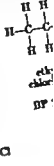
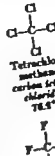
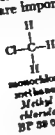
**Sulphone Methanes**—Three important compounds exist in this group: *Sulphonal*, *trialonal*, and *tribronal*.

The sulphone methanes are little used clinically because they are feeble hypnotics. They dissolve in water with difficulty and possess cumulative properties.

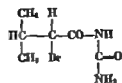
**AMIDES**—Amides may be considered as ammonia with one of its hydrogen atoms replaced by an acyl radical. They may also be considered as carboxylic acids with the hydroxyl group replaced by an amino group. Certain amides possess hypnotic and sedative actions. Amides are non-volatile drugs.

**Substituted Aliphatic Amides**—The amides have no depressant effects unless the hydrogen atoms are substituted by aliphatic aromatic and other groups. None of this group is employed clinically.

**Urethanes**—Carbonic acid, the anionamide of carbonic acid, forms esters with various aliphatic alcohols. This group of esters is known as urethanes. Ethyl urethane or *ethyl urethane*, *hexameth*, and *spinal* have been used clinically. Potency of urethanes increases as molecular weight increases. Urethanes formed from primary alcohols are less potent than those formed from secondary or tertiary. Ethyl urethane, *hexameth* and *spinal* are important urethanes.



**SUBSTITUTED UREAS**—Urea the di amide of carbonic acid possesses no depressant action. Substitution of the hydrogens of the amino groups by alkyl, aromatic, aryl, and other radicals produces a large series of hypnotic derivatives.



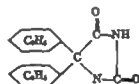
*Bromacetal*  
bromo-iso valeryl urea



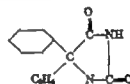
*Carbonal*  
bromo-diethyl acetyl urea

**UREIDES**—Urea reacts with carboxylic acids to form compounds known as ureides and water. Monocarboxylic acids form open chain ureides. Dicarboxylic and other acids with two acidic groups form cyclic ureides. Two groups of cyclic ureides are important as central nervous system depressants—the hydantoin and the barbiturates.

**Hydantoins**—These are derived by condensation of glyoxylic acid with urea. The five membered glycoalkyl urea gives rise to two important anti-convulsants, dilantin and nirvanol, by substitution of the two hydrogens on the 5 position with aromatic and alkyl groups.



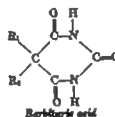
*Diphenyl hydantoin*  
(dilantin)



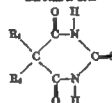
*Phenyl ethyl hydantoin*  
(nirvanol)

**Barbiturates**—These are derived by condensation of urea and malonic acid. The malonyl urea which forms is a six membered cyclic structure which gives rise to many hundred compounds if substitutions are made on the various atoms of the ring. Substitution of the two hydrogen atoms on the 5 position by alkyl, aromatic, aliphatic and other radicals yields some of the most useful sedative and hypnotic drugs used in clinical medicine.

**Thio-barbiturates**—Condensation of thiourea with malonic acid gives rise to a series of derivatives known as thio-barbiturates. These are similar to barbiturates with the exception that the oxygen atom is replaced by sulphur. Thiobarbital is the most important member of this group.



*Barbituric acid*



**MISCELLANEOUS SYNTHETIC HETEROCYCLIC AND AROMATIC ANALGESICS**—Derivatives of piperidine (demerol) heptanone (methadon) ethylene diamine (anti-histamine drugs) aromatic amines (ephedrine), complex basic esters (atropine syntropin etc.) derivatives of cyclopentenophenanthrene (various hormones) possess either general or local anesthetic action. The most important members of this group are methadon and demerol.

**ALKALOIDS**—Alkaloids are nitrogen containing substances elaborated by plants. The nitrogen usually in the form of a primary secondary or tertiary amine confers basic properties to the compounds. Alkaloids are usually aromatic, aliphatic or heterocyclic compounds. They are unique because minute amounts produce physiological activity. They form salts with inorganic and organic acids. Alkaloids possess optical activity. The alkaloids derived from opium are the only central nervous system depressants of clinical importance. Alkaloids of the coca plant are useful local anesthetic drugs (cocaine). Numerous synthetic substances similar in properties and reactions to alkaloids have been prepared. Many alkaloids formerly obtained from plants are now prepared synthetically.

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

## RELATION OF PHYSICAL AND CHEMICAL BEHAVIOR TO DEPRESSANT EFFECTS ON THE CELL

Depressant drugs exhibit a variety of chemical and physical properties in artificially prepared systems in vitro designed to simulate protoplasm. Similar behavior is believed to occur in the living cell.

**Water Solubility**—Volatile agents, as a rule, are poorly soluble. Useful non-volatile agents are soluble. All drugs must possess some water solubility to be carried to the cell. The majority of drugs are more soluble in blood than in water but partition exist between solubility in the two. Water solubility serves as an index of blood solubility.

**Lipoid Solubility**—Most drugs are highly soluble or miscible in oils and lipoids. A partition exist between solubility in lipoids and the quantity absorbed by nerve tissues since nerve cells are rich in lipid substances.

**Oil Water Ratio**—Ratio of partition of the drug between equal volumes of oil and water at 37.5°C. Drugs possessing ratios of high magnitude are known as lipophilic agents. For the most part potency parallel increases in magnitude of this coefficient.

**Lipoids**—Lipophilic anesthetics are absorbed by cells rich in lipid (nerve and adipose tissue). Therefore, they are more potentiated with drugs possessing high oil-water coefficients. Lipids in the cell membrane may be altered by the drug and permeability thereby affected.

**Stability**—Most potent agents are inert or destroyed slowly in the cell. Ether, cyclopropane, ethylene, etc. are not altered by intracellular biochemical processes.

**Intracellular Fluids**—Water content of cell is decreased during depression induced by drugs. Fluids transude outward. The reaction is reversible. Viscosity is increased. Intracellular pH is decreased.

**Physical Phenomena**—Negative electrical polarity is decreased or reversed on nerve cells during narcosis. Electroencephalogram altered.

**Colloids**—Protoplasm is colloidal in nature. Colloidal properties are due to proteins. Proteins are coagulated by depressant agents. Colloidal particles, because of their smallness and the fine division, present a large surface to the dispersion medium.

**Adsorption**—Many depressant drugs are adsorbed on surfaces of activated substances such as charcoal. The large surface possessed by particles in colloidal solution favors adsorption.

**Surface Tension**—Many drugs decrease surface tension of water at room temperature. Similar decrease or decrease in interfacial tension may occur in protoplasm.

**Viscosity**—Viscosity of colloidal flows is increased by many drugs. Changes in viscosity may cause decrease in permeability of cell membrane.

**Enzyme Activity**—Many drugs decrease enzyme activity, particularly those which facilitate oxygen utilization such as oxidases and dehydrogenases.

## EFFECTS OF DEPRESSANT DRUGS ON CELLS AND TISSUES

**Cell Membrane**—Cell permeability is decreased by depressant drugs. Change in permeability may be due to:

1. Adsorption of drugs on constituents of the membrane.
2. Reduction in surface tension.
3. Alteration in constituents of the membrane.
4. Increase in viscosity of the membrane.

**Colloids**—An ultra microscopic coagulation or flocculation of protein may occur. Large concentrations of depressant drugs cause clumping of cytoplasm thought to be precipitation. Reptilation or reversal occurs upon removal of the drug. (Claude Bernard-Baeretz).

**Metabolism**—Carbohydrate metabolism of nervous tissues is depressed. Dehydrogenases are inhibited by many depressant drugs in vitro. Oxygen consumption is reduced.

**Tolerance** develops to depressant drugs. Repeated use causes habituation or psychic craving. Addiction (physical dependence) manifested physiological disturbances may result. This is due to inability of the cell to function unless drug is present.

Depressant drugs possess three characteristic features (1) They depress all types of cells (2) they have a special predilection for nervous tissue (3) the action is reversible and the cells return to normal when the drug is removed from the cell.

## THEORIES OF NARCOSIS

Narcosis is a reversible reduction of cell activity produced by physical or chemical agents. Physical agents such as cold, electricity or pressure may also reduce cellular activity. Chemical substances, both inorganic and organic, known as anesthetics, hypnotics and sedatives likewise reduce cellular activity. No definite mechanism has been decided upon. The following theories, based upon chemical, physicochemical or physical changes occurring in biological systems have been propounded.

Base of Theory	Year	Proposition	Proposer	Evidence	Objection
Lipoid solubility	1847	All fat solvents are narcotics. They cause narcosis by washing lipoids out of cells.	Bohn & Harless	Blood lipid increases during anesthesia. Lipoid content of certain cells reduced.	Recovery occurs too rapidly to account for return of lipid into the cell.
	1896	Narcotic substances exert a direct reaction on cellular lipoids.	Hermann	Aliphatic hypnotics dissolve in red blood cells because they are highly soluble in lipoids and lipoids are abundant in these cells.	Solubility in water not same as blood and lymph. Work done on olive oil and oils not similar to body fats. Applies to aliphatic compounds only and does not include or explain action of heterocyclic substances, alkaloids and inorganic substances. Explains mode of transport to nerve thames but not its action in cell. Oil, water ratio not a true index of amount absorbed by thames.
	1895		Richert		
	1890	Narcotic efficiency parallels coefficient of partition between oil and water. Lipoids in cell and on cell membrane absorb drug because of this great affinity.	Meyer	Narcotic potency of aliphatic compound increases as coefficient of partition between oil and water increases.	
	1901		Overton		
			K. Meyer	Concentration in moles per liter of drug which causes narcosis is constant and averages 0.58 moles/liter.	
Surface affinity of drugs (Surface tension)	1904	Substances which lower surface tension of water pass more readily into the cell and cause narcosis by decreasing metabolism.	Treane Campbell	Parallelism exists between ability of drugs to lower surface tension of water and their narcotic potency.	Experiments were done on air/water interfaces at room temperature. Should be done on two liquid interfaces at body temperature. Many exceptions-chloroform and ethyl alcohol.
Adsorption	1930	Drug becomes concentrated at the surface of the cell due to adsorption. Drug may then alter permeability and alter metabolism.	King Also data by Lillie Warburg and Jilber	Narcotic activity of certain drugs parallels amount of substance adsorbed at paraffin water interface. Certain drugs applied to surface of anesthetic cause depression of activity. None if injected directly into cell.	Most of experiments have been done on artificial systems or in vitro. Duplication of results in higher forms of life not successful.
Changes in permeability of cell membranes	1912	Permeability of cell membranes decreased by narcotic concentrations of aliphatic and other central nervous system depressants. Toxic concentrations increase permeability.	Lillie Höber	Low concentrations of aliphatic substances added to aqueous media prevent swelling of nerve and muscle cells in hypertonic solutions.	Most experiments result of in vitro studies or from studies on structures of lower forms of life.
	1913		Winterstein	Lipoids concentrate at cell membrane because they lower surface tension. Drugs pass into lipid in cell membrane, cytoplasm and decrease permeability and reduce metabolic activity.	

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

10

Basic Theory	Year	Proposition	Proposer	Evidence	Objection
Changes in colloid of cell (1) Coagulation or flocculation of protein.	1857	Coagulation or flocculation of protein causes dehydration and reduction of metabolisms.	Ranke	Noted clumping of muscle cells by chloroform which he thought was coagulation of proteins.	Concentrations necessary to cause coagulation experimentally greater than those encountered clinically. Experiments done on tissue systems in vitro or on the lower forms of life.
	1873		Blaiz	Noted changes in transparency of cytoplasm of nerve cells after exposure to chloral and morphine.	
	1888		Claude Bernard	Fluid narcosis due to reversible semi-coagulation of protein of cytoplasm of cell.	*Narcosis does not always follow dehydration and fluid loss in cell.
	1907		Dehols	Noted shrinkage of cells due to loss of fluid following exposure to depressants.	
	1907		Höber	Noted shrinkage of cells due to water loss from cell following exposure to depressants.	
	1907		Bancroft	Ultra microscopic reversible coagulation occurs which is visible with ultra microscope.	
	1907		Elbeek	Drugs alter protein and increase viscosity of cytoplasm.	
(b) Increase in viscosity (c) Combination with proteins of cell.	1907	*Narcotic combines with protein and other constituents of protoplasm. Drug becomes loosely adsorbed on colloids.	Moore & Ross	Amount of chloroform in blood greater than physical laws of solubility allow.	Amount of chloroform required produces effect greater than necessary for narcosis.
	1907		Mathews-Brown	None	*No experimental data.
	1907		Baghoni	None	Anaesthesia and narcosis are not similar.
Decrease in cellular oxidation	1907	Excess carbonates which was thought to play role in cellular oxidation inhibited by narcotics.	Verwoerd	Narcosis is accompanied by diminished oxidation.	Diminished oxidation is the result and not the cause of narcosis. Narcotics do not interfere with accessibility of oxygen to the cell.
	1907	Depressant drugs interfere with tissue oxidation.	Warburg	Activated charcoal adsorbs organic acid which in turn oxidized. Anaesthetics inhibit this oxidation.	Data obtained from in vitro experiments on a purely physical system.
	1907	Narcotics cause oxygen deprivation which causes cell to be narcotized.	Quastel, Wharely and Janet	Oxygen consumption of brain slices on microrespirometer reduced because of decreased oxidation of glucose lactate and pyruvate.	Are in vitro studies on carbon tissues. Anaesthetics metabolize in tissues. Anaesthetics in tissues reduce availability and thereby decrease oxidation. Suppression of oxidation could be result of narcosis and not cause.
(a) Oxygen deprivation.	1907		Bergs, Derbyshire, Bremer and others	Reversal of polarity of cortex in relation to electric nerve occurs during narcosis.	Description of the phenomenon of cortex rather than explains it.
(b) Narcotics inhibit oxidation.	1907		Wulf, Featherstone		Many exceptions. Chole should be weaker than it causes molecule is similar.
(c) Inhibition of respiratory enzymes. (d) Suppression of formation of high energy phosphate bonds.	1907		Ferguson, Mullins	Mathematical and physico-chemical in laboratory.	
Electrical potentials of nervous tissue altered by narcotic drugs. Polarity reversed.	1907	Action potentials on brain tissue observed under narcotic drugs similar to those of normal sleep.			
	1907	Molecular volume			
Thermodynamic activity	1907	Rebels molecular volume determined by Wulf constants			
	1907	Interposition of narcotics molecules in aqueous cellular phase causes changes which interfere with facilitation and ionic exchange			

## SECTION II. ADMINISTRATION, ABSORPTION, AND ELIMINATION OF ANESTHETIC DRUGS

### ROUTES OF ADMINISTRATION OF DRUGS

**Subcutaneous Route**—Useful for non-volatile water or oil soluble hypnotic and narcotic drugs. Not satisfactory for administration of irritating drugs which may cause abscess. Rate of absorption varies with blood supply to the tissue. Slow absorption occurs from subcutaneous fat due to poor blood supply to this tissue. Oily solutions used for continuous slow absorption.

**Intra-muscular Route**—Useful for irritating drugs, drugs dissolved in oil or aqueous solutions to be rapidly absorbed. Excellent blood supply to muscle tissue favors rapid absorption. Absorption slow in shock or hypotension from other causes.

**Intravenous Route**—Useful for water soluble anesthetics, hypnotic and narcotic drugs. Factors which modify absorption by other routes are not present in this method. Desired blood concentration is promptly obtained. His disadvantage of being non-controllable i.e. blood concentration cannot be varied or reduced in event of overdosage. Also drug may pass from blood and be stored in tissues causing cumulative action.

**Intra-medullary Route**—Useful when veins are not accessible. Sternum is used for adults, long bones for infants. Drug passes into venous circulation with almost same speed as if directly injected into the veins.

**Intra-arterial Route**—Not suitable. Spasm of artery and its tributaries may result in gangrene or other damage characteristic of ischemia.

**Topical Route**—No appreciable absorption occurs through the skin. Local anesthetic drugs pass through and anesthetize the mucous membranes of the nose, throat, trachea, bronchi, urethra, vagina, rectum, bladder, oesophagus and stomach.

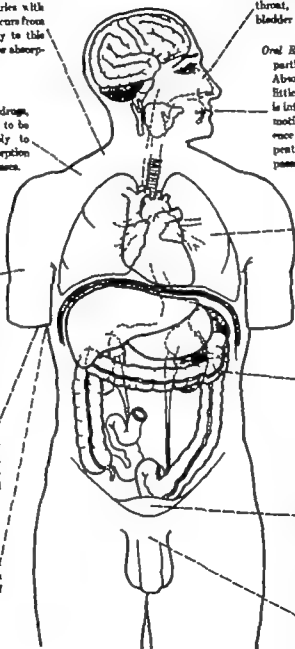
**Oral Route**—Useful for non-volatile soluble drugs, particularly analgesics, hypnotics, and narcotics. Absorption is mostly from the small intestine. Little if any occurs from the stomach. Absorption is influenced by variable factors such as intestinal motility, pH of intestinal contents, and the presence of other substances. Some drugs, such as penicillin and eripal, are rapidly destroyed on passage through the gastro-intestinal tract.

**Pulmonary Route**—Useful for gases and liquids which volatilize below 60°C. Gases and vapors gain access to blood by diffusion into the pulmonary capillaries through the alveolar membrane. Drug is carried to left heart and thence to the tissues.

**Intraperitoneal Route**—Useful for non-irritating non-volatile hypnotic and narcotic drugs. Large serous surface favors almost immediate absorption. Drug passes into lymphatics. Absorption greater in area around diaphragm. Used in animals. Danger of adhesions and infection precludes use in man.

**Intrathecal Route**—Useful for water soluble local anesthetic drugs to block nerve conduction. Drug slowly passes into venous circulation from spinal fluid.

**Rectal Route**—Useful for either volatile or non-volatile drugs. Vegetable or mineral oils are often used as vehicles for lipoid soluble drugs. Absorption proceeds almost entirely from the rectum unless ileocecal valve is patent. Absorbed drugs pass through the liver which may cause modification or temporarily store them before passing into the systemic venous circulation.







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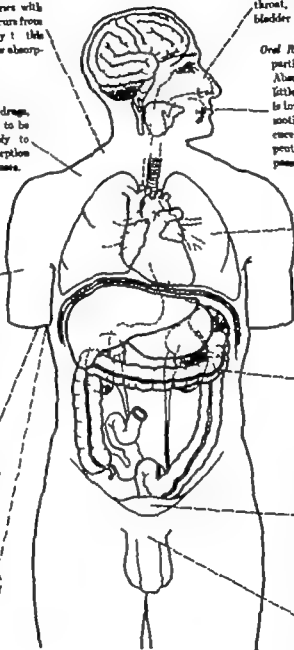
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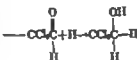
## DETOXIFICATION OF DEPRESSANT DRUGS

Detoxification is the conversion of a physiologically active substance to one which is less active or inactive. Although many tissues are capable of detoxifying drugs, the liver plays the dominant role in the process. Detoxification varies with the concentration of drug and the state of organism. Most drugs are detoxified by one or a combination of several of the following biochemical mechanisms:

**Oxidation**—The drug is combined with oxygen and converted to various intermediate products or even completely oxidized to carbon dioxide and water. Energy in the form of heat is liberated. Alcohols are detoxified in this manner. Ethyl alcohol is converted to carbon dioxide and water. Each gram liberates seven calories of heat.



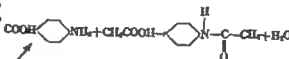
**Reduction**—This is the converse of oxidation. It is accomplished by the addition of hydrogen. Aldehydes may be detected in this manner. Chloral, which is an aldehyde, is reduced to trichloroethanol, an alcohol.



**Hydrolysis**—Esters and other compounds capable of adding a hydrogen atom and a hydroxyl group are detoxified in this manner. Procaine is hydrolyzed to an acid (para amino benzoic acid) and an alcohol (diethyl amine ethanol). The compound is split through the action of water to two or more compounds.



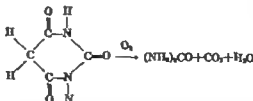
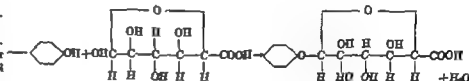
**Conjugation**—The drug is altered by combining it with another compound or radical to form a new derivative which is inert or less active. Acids, amino acids or the methyl radical are used for combination. The conjugating substance is usually derived from some endogenous source.



**Acetic Acid**—Used to add the acetyl group to amine compounds. Para amino benzoic acid, which is derived from procaine is changed to acetyl amino benzoic acid.

**Cysteine**—Used to detectify halogenated compounds.  
**Sulphonic Acid**—Used for conjugation with phenols.  
 Phenol combines with it to form indoxyl.

**Glyceric Acid**—Forms glycosides with alcohols as esters with acids. Tribromethanol, trichloroethanol and chloral are converted to glycoside type compounds in this manner.



**Degradation**—I certain cyclic compounds side chains are removed and the ring is disrupted so that no trace is found in the body. Barbiturates are decomposed in this manner. The exact mechanism is not known.

More than one mechanism may be employed in the detoxification and elimination of a drug. Ethyl alcohol is oxidized in the liver if concentrations are low. Some is eliminated unchanged in exhalations and urine and some is detoxified if blood concentrations are high. Species variations are common. Aniline hydrate is conjugated with glucuronic acid in rats, and eliminated unchanged in man. Various enzymes, such as esterases, oxidases, dehydrogenases, may assist in the detoxification. The blood contains an esterase which hydrolyzes procaine.



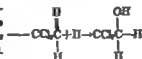
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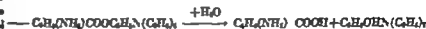
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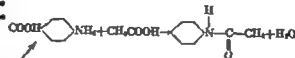
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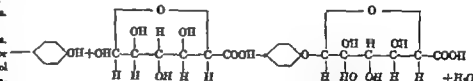
**Cytrinic**—Used to detoxify halogenated compounds.

**Sulphuric Acid**—Used for conjugation with phenols.

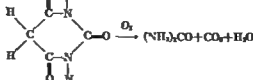
Phenol combines with it to form indoxyl.

**Glycine**—Used for conjugation with aromatic acids.

**Glyceric Acid**—Forms glycosides with alcohols or esters with acids. Trichloroethanol, trichloroethanol and chloral are converted to a glycoside type compound in this manner.



**Depolymerization**—In certain cyclic compounds side chains are removed and the ring is disrupted so that no trace is found in the body. Barbiturates are decomposed in this manner. The exact mechanism is not known.



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## SECTION III. GENERAL SYSTEMIC EFFECTS

### EFFECT OF CENTRAL NERVOUS SYSTEM DEPRESSANTS ON VARIOUS ORGANS

**Brain**—Depressed from above downward. Progressive depression results in paralysis of medullary centers. Respiratory center fails first usually.

**Spinal Cord**—Not affected until concentration causing medullary depression has been attained.

**Laryngopharynx**—No histological effect. susceptible to anesthetic concentrations of gaseous or volatile drugs. Respiration stimulated by some agents (ethers, halogenated hydrocarbons) by irritation, no effect by others until medullary depression occurs (cyclopropane, barbiturates).

**Diaphragm**—Usually last of respiratory muscles to be paralyzed.

**Mriothorax**—Depressed during anesthesia and hypoxia with most agents due to decreased activity.

**Laryngopharynx**—Increased respiratory activity with some agents causes absorption from lymphatics of peritoneal cavity and diaphragm.

**Peripheral Nerves**—Action potentials unaltered until deeper phases of anesthesia are reached with most agents.

**Muscles**—Potent inhalation anesthetics cause loss of tone from central depression. Small agents (nitrous oxide and ethylene) do not affect tone appreciably. Paralysis of smaller muscles precedes that of larger muscles. Complete loss of muscle tone contributes to circulatory failure by diminishing venous return to heart (spinal anesthesia, curare).

**Salivary Glands**—May be stimulated during induction and are inhibited anesthetics—ether, chloroform, cyclopropane. Depressing anesthetics. Effect non-volatile substances depends from the site.

**Teeth**—Salivary glands stimulated by volatile. Little affected by the gases and non-volatile.

**Thyroid Gland**—Not significantly affected by most drugs.

**Lungs**—Locally irritated into spasm by drugs (ether, ethyl chloride). Centrally affected (cyclopropane, protodol) not affected by most agents.

**CNS**—Activity depressed by most and non-volatile agents.

**Heart**—Myocardium seldom depressed in anesthetic concentrations except by certain nitro hydrocarbons (like ethyl chloride). Certain agents increase irritability of conduction system (cyclopropane, ethyl trichloroethylene).

**Bronchi**—Dilated by some chloroform, ether. Constrict others—cyclopropane, gas. No effect by others—nitrous oxide, ethylene.

**Autonomic Nervous System**—Effects of stimulation with some agents ether, form, thiopentone are sympathetic. Cyclopropane and barbiturates are parasympathetic. No effect by others (nitrous oxide, ethylene).

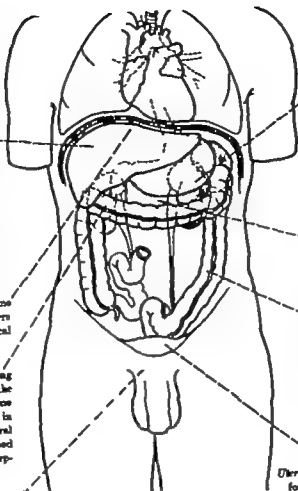
**Blood**—Hemoconcentration caused by most. Hemodilution low common (barbiturates). Volume reduced. Morphology of cells not affected. Acid base balance disturbed by some agents (chloroform) unchanged by others (cyclopropane, ethylene, nitrous oxide). Glucose increased mobilization of liver glycogen by some agents (chloroform). Nitrogenous elements unchanged. Urea mechanism not disturbed.

**Liver**—Ability of liver to excrete is most frequently studied function. Clearance of bromsulphalein is test most commonly used. Some cause no depression—cyclopropane, nitrous oxide, ethylene, barbiturates. Others cause profound effect—ether, chloroform. Anoxia superimposed on anesthesia causes profound changes. Local and spinal anesthesia no change. Bile flow not impaired by most agents. Chloroform and anoxia do impair. Glycogen stores depleted by sympathomimetic drugs—ether, chloroform, anoxia. Urea formation not impaired. Ability of synthesis hippuric acid impaired by some agents. Prothrombin time not affected by any except chloroform.

**Adrenal**—Some cause depletion of epinephrine in the gland—ether, chloroform. Others cause no effect. No notable effect on cortical hormones recognized.

**Kidney**—Urinary output suppressed during anoxia by most depressants. Probably the result of release of antidiuretic hormone from pituitary. Also affected by changes in blood pressure, renal blood flow, general fluid loss, (retaining, bleeding, etc.) blood electrolyte changes and decreased absorption from gastrointestinal tract.

**Bladder**—Atony with increased bladder volume follows depression of smooth muscle by some agents. Loss of sensation and desire to void further increases atony and contributes to post-operative urinary retention.



**Spleen**—Constricted by sympathomimetic drugs, anoxia and anesthetics which stimulate sympathomimetic action—ether and chloroform. Dilated during cyclopropane and spinal anesthesia. Blood flow need not be affected even though volume is decreased. Effect on pathological spleen with mesh fibrosis not pronounced. Changes in spleen volume reflected in blood and red cell volume. Enlarged when hemodilution occurs—barbiturates.

**Pancreas**—Inhibition of insulin action and production may occur—ether

**Gastrointestinal Tract**—Potent anesthetics such as ether and chloroform inhibit activity absorption and secretion and reduce peristalsis. Milder drugs such as nitrous oxide, ethylene have little or no effect. Crytotoxins are spasmolytic—morphine, ether. Others are spasmolytic—demerol. Part of inhibiting action may be due to autonomic effects and part due to direct action on muscle.

**Uterus**—Major anesthetics such as ether and chloroform depress activity and motility. Depression progressive with depth of anesthesia. Mild anesthetics—nitrous oxide, ethylene, vinyl ether—have little effect. Spasmolytic substances such as morphine inhibit motility and increase tone. Drugs pass through placenta.

## VOLATILE VERSUS NON VOLATILE DRUGS

Central nervous system depressants are classed as volatile or non-volatile. Each type has certain physical and pharmacologic characteristics common to the group as a whole. Volatile liquids whose vapor pressures at room temperature are sufficient to produce adequate blood tensions for anesthesia when inhaled are classed with non-volatile drugs (alcohol).

General characteristics of volatile drugs are:

1. They are inert in the body and are eliminated unchanged.
2. Vapor pressures at room temperature are sufficient to produce narcotics when inhaled.
3. The tension in the brain necessary for anesthesia varies with the arterial tension. Arterial tensions are suitable indices of depth of anesthesia.
4. Are complete anesthetics. They possess analgesic properties and abolish transmission of impulses from the periphery to the higher centers (block transference-thalamic pathways and reticular activating system).
5. They are poorly soluble in water (hydrophobic) and highly soluble in lipoids (lipophilic).
6. Variations in reflex activity (signs of Guedel) may be used as a guide to depth of anesthesia.
7. Provide controlled anesthesia. Tension in the brain may be altered at will by varying the arterial tension by changing the inhaled concentration or by washout, using artificial respiration.
8. The respiratory center is depressed before other vital centers. Respiratory depression or apnea may occur before circulatory changes occur.
9. They may augment ventilation by local effects on pulmonary stretch and deflation receptors.
10. They cause reproducible changes in electroencephalographic pattern which vary with arterial tension of drug. Changes, therefore, serve as guide to depth of anesthesia.

Non-volatile drugs:

1. Do not completely interrupt pathways from periphery to the central receptors. Reflexes remain active.
2. Must be administered by routes other than inhalation. When administered parenterally ill-effects may ensue due to sudden perfusion of organs with a foreign substance.
3. Must be detoxified or are eliminated unchanged. This may require a long time.
4. Are not controllable. Must be administered in pre-determined doses. Once an estimated dose has been administered, it cannot be retrieved.
5. Delayed effects appear due to accumulation of breakdown products.
6. Blood plasma levels not an index of total concentration in body or brain.
7. May be bound to protein in plasma which inactivates them.
8. Depress all the vital centers simultaneously or the circulatory centers, at times, before respiratory.
9. Reduce completely alveolar pulmonary, tracheal and bronchial reflexes.
10. Nullify signs of anesthesia (Guedel).
11. May manifest untoward responses, such as intolerance, allergy.
12. May cause postoperative disorientation.
13. Are not analgesic. Are usually not adequate as sole anesthetics. Must be used in combination with drugs.
14. Do not stimulate local reflexes in mediation of ventilatory exchange.



# THE PHARMACOLOGY OF ANESTHETIC DRUGS

## GENERAL EFFECTS ON THE CENTRAL NERVOUS SYSTEM

**I FIRST STAGE**—Analgesia—Due to depression of higher cerebral centers.

**III THIRD STAGE**—Surgical—Automatic lower centers remain active but released from cortical control.

- (1) First plane—Spinal reflexes disappear
- (2) Second plane—Muscle tone decreased.
- (3) Third plane—Complete intercostal paralysis.
- (4) Fourth plane—Complete loss of muscle tone and reflexes.

**Cortex**—Most highly developed functions disappear first.  
Higher activities depressed—II  
Motor areas slightly depressed—II  
Sensory areas depressed—II  
Inhibitory centers depressed—II  
Motor areas further depressed—III  
Occipital lobe depressed—III  
Frontal convolutions depressed—III

**Cerebral Areas**—Olfactory area depressed—I  
Sense of smell disappears before hearing or sight.  
Auditory area not affected—I  
Slightly depressed—II  
Depressed—III, (1)

**Medullary Centers**—Respiratory centers depressed—III  
Threshold to CO<sub>2</sub> lowered.  
Does not respond to CO<sub>2</sub>—IV  
Respiratory movements cease before  
circulatory in most and some.

Cough center depressed—III, (1)  
Vomiting center depressed—III, (1) and IV  
Medullary paralysis—III, (1) and IV

**Facomotor Center**—Depressed III, IV  
Unchanged I.

**Re. position**—Rate and movement unchanged—I.  
Irregular depth may increase—II, due to  
release of inhibition of cerebral and sub-  
cortical centers.

Regular respiration—III (1)  
Lower intercostal lag—III (2)-(3)  
Expiration longer than inspiration—III, (4)  
Diaphragmatic respiration—III (3) (4)  
Central respiratory paralysis—IV  
Hering-Breuer reflex remains active

**Card**—Depressed after medulla.

**Automatic Nervous System**—Remains active  
Instability may occur with some agents  
giving resemblance of sympathomimetic ac-  
tion (ether) or parasympathomimetic ac-  
tion (cyclopropane)

**Motor Nerves**—Action currents remain active I,  
II, III  
red nucleus depressed—II

**Skeletal Muscles**—Tone increased—III, (1)  
Small muscles relaxed—III, (4)  
Large muscles relaxed—III (2), (4)  
Complete relaxation—III (2), (4)  
Diaphragm paralyzed—III (4)

**II SECOND STAGE**—Delirium or "excitement"—Cere-  
bration depressed.

**IV FOURTH STAGE**—Overdose—An irregular delirium  
involving in succession the cortex, lateral geniculi, cerebellum  
and oculi centers. Signs are modified by premedication, an-  
dioxide, curare, bark, etc.

**Thalamus**—Corticothalamic fibers interrupted—III  
Basal ganglia depressed after the cortex.

**Temporary Regulating Center**—Depressed  
Vain Standard.  
Cerebration—Depressed after the basal ganglia.

**Eye**—Right disappears before le-  
ft—II  
Pupillary reaction to light un-  
changed—I  
Eyeball movement unchanged—I  
Pupils dilated, movements and re-  
flexes unchanged—II  
Voluntary control of lid remains.  
Lid reflex disappears—III (1)  
Pupils contract—III, (1)  
Motor control unchanged—III, (1)  
Pupils in mid-contraction, no  
reflexes slightly depressed—III,  
Pupils in mid-dilation, no  
reflexes abolished—III, (4).  
Pupils dilated and irregular—  
(4) and IV  
Corneal reflex disappears—III  
Tear secretion depressed—III  
Disappears—III, (1).

**Pharynx**—"Gag" reflex disappears—III, (1).  
Oro-pharyngeal—III, (4).

**Larynx**—Laryngeal reflex disappears—III,  
(4)

**Esophagus**—Cough reflex disappears III, (5)  
in large bronchi and III, (4) in smaller  
**Heart**—Rate increased (excitement)—II.  
Decreases to maintenance rate—III, (1).  
Rate varies.

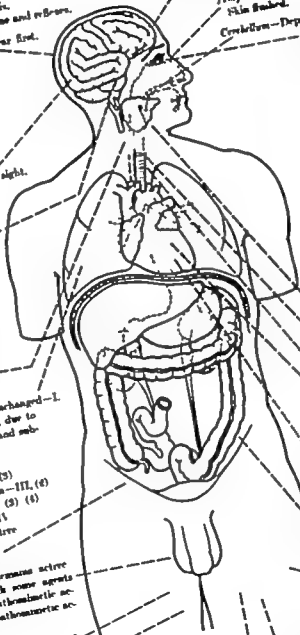
**Blood Pressure**—Unchanged—I.  
Increased (excitement)—II.  
Returns to normal—III, (1)-(3).  
Fall—III, (3)-(4) and IV. Due to medullary  
paralysis or effect on cardiovascular system.

**Venous Pressure**—No change—I.  
Rises, due to increased muscle tone—II. Is  
unchanged in IV. Increases in IV.

**Breathing**—Analgesia—I (skin sensation dis-  
appears, various body areas in the following:  
back, extremities, genitalia, face) Motor  
remains active

**Deep Reflexes**—Active III, (1), (4) (5)  
Obtunded IV

**Superficial Reflexes**—Active—I Exaggerated II.  
Obtunded III, (1).



## EFFECTS ON RESPIRATORY SYSTEM

**Cerebrum**—Effects from psychic stimulation removed during anesthesia. Voluntary control of respiration lost. Rhythm becomes regular.

**Sub-cerebral Centers**—Effects not well-defined or studied. May cause irregular breathing in stage II.

**Medullary Centers**—Respiratory center depressed in lower stage III and in IV. Respiratory center consists of formative reticularity, a group of neurons, both motor and sensory, which are inter-connected by fibers which control various parts of respiratory system. Cells very sensitive to  $\text{CO}_2$  and  $\text{H}^+$ . Variations in sensitivity between individual neurons exist; more sensitive neurons resistant to depressant drugs. Center sends rhythmic impulses to adjacent vagal and other vital centers. Deleterious action as one center may influence other centers in medulla and lower cord.

**Vagus**—Hering-Breuer reflex remains intact. Reflex inhibits inspiration during overdistension and inhibits expiration if negative pressure is applied to alveoli.

**Carotid-arterial Chemoreceptors**—Composed of a group of cells sensitive to blood chemical changes (anoxia). Reflexly stimulates respiration when  $\text{O}_2$  tension is lowered. Usually depressed by anesthesia. Receptor cells more resistant than cells of respiratory center. Apnea may result in presence of depressed medulla or apnea when anoxic stimulus is removed with high  $\text{O}_2$  tension.

**Phrenic**—Diaphragm is chief muscle of respiration. Last to be paralyzed. Controlled by sensitive neurons of center which send impulses to the phrenic nerve.

**Reflexes**—Manipulation and stimulation of the following structures during anesthesia causes disturbances in rate and rhythm of respiratory movements. (Reflexes suppressed after structures)

1. **Alveoli**—Stimulation increases rate, sometimes depth.
2. **Peritoneal**—Rub peritoneal stimulation causes inhibition or even apnea with some great.
3. **Rectal**—Distention of rectal sphincter increases rate and depth, especially in light planes also stimulation of perineum and genitalia.
4. **Perineal**—Traction on perineum results in spasm of larynx (Biering-Lachmann reflex). Frequent with traction on gallbladder, stomach, spleen or kidney.
5. **Perineal**—Stimulation increases rate and depth.
6. **Plural**—Manipulation of pleura often inhibits respiration or causes coughing.
7. **Uterine**—Stimulation of uterus or bronchi induces coughing or bronchial spasm.
8. **Esophageal**—Stretching or manipulation of wall causes inhibition of respiration (also arthylaxia).

**Intracranial Pressure**—Depressant drugs, anoxia and carbon dioxide excess increase intracranial pressure. May indirectly affect respiration by pressure on medulla.

**Mucosa**—High concentrations may irritate and promote secretions. May also inhibit respiration reflexly.

**Muscles**—Tongue and neck muscles relax and may cause airway to become obstructed. Accessory muscles of respiration concerned; less sensitive neurons. Are depressed easily by most drugs.

**Cilia**—Ciliary activity first stimulated then halted by depressant (both volatile and non-volatile) drugs. Some drugs depress directly and cause bacteria from upper tract to pass to lower tract.

**Pharynx**—Stretching of muscles and pharyngeal wall by catheters and air ways stimulates respiration.

**Larynx**—Irritating concentrations of volatile drugs, mucus, vomitus, blood and alkaline doses produce apnea. Reflex spasm may result from stimulation of interconnecting parts of nervous system. Drugs may stimulate or depress laryngeal nerves. Bronchial spasm may result if stimulation is excessive.

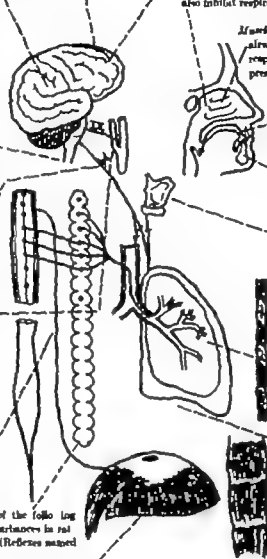
**Respiratory Exchange**—Minute volume exchange decreased from decreased metabolism as well as central depression. Decreased activity decreases blood pressure; retards venous return.

**Intracranial Muscles**—Controlled by more sensitive and more resistant neurons of respiratory center. Lower intercostals paralyzed first. Reciprocal innervation exists between inspiratory and expiratory nerves so that one inhibits while the other is active.

**Alveolar Membrane**—Not altered histologically. Local stimulation by irritating vapors and gases increases respiratory volume and rate by affecting vagal endings (vagus). Volatile drugs readily pass through membrane.

**Abdominal Muscles**—Loss of tone retards venous return to heart. Surgery of upper abdomen results in splinting of upper thorax. Decreases exchange postoperatively. May contribute to atelectasis.

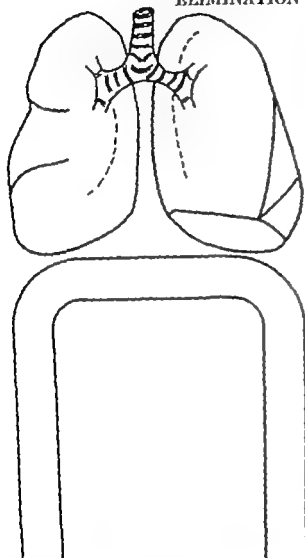
**Tissue Respiration**—Drugs may inhibit dehydrogenase and reduce metabolic activity and oxygen consumption.





## SECTION IV ADMINISTRATION OF VOLATILE DRUGS

### FACTORS INFLUENCING ABSORPTION AND ELIMINATION OF VOLATILE DRUGS



**Concentration of Drug in Inhaled Mixture**—Usually expressed in volumes per cent or partial pressure in atm of 760. High partial pressure establishes a steep gradient from lungs to blood and rapid saturation results. Pressure gradient reversed during recovery. High concentration in blood—low in alveoli. Elimination rapid at first and gradually tapers off as pressure gradient falls.

**Tidal Volume**—Directly affects the amount of drug inhaled per unit time. High values with the functional residual air. Shallow breathing causes slow mixing and prolonged induction. Rapid, deep breathing hastens induction by increasing amount of drug in the alveolar air. Approximately two-thirds of normal tidal volume mixed with alveolar gases.

**Functional Residual Air**—Represents air space in lungs in contact with alveolar surface. Total volume small in children. Sudden, deep inspiration causes rapid mixing and deepening of anesthetic (or lightening if air is inhaled). Abnormally excessive in emphysema and related diseases. Mixing then occurs slowly. Saturation and desaturation of blood are slowed.

**Solubility in Blood**—Amount which dissolves in blood is in direct proportion to partial pressure. Maximum amount which dissolves depends on solubility coefficient (air-blood ratio) at body temperature.

**Permeability of Alveolar Membrane**—Gases pass in either direction through the membrane. Diffusion depends upon facility of passage of gas or vapor through a liquid. Also a selective permeability exists. Currently used drugs readily pass through and cause no histological alteration of epithelium. Secretions, Starvation, inflammation and edema interfere with absorption of gases by reducing alveolar surface.

**Blood Flow through Lung Capillaries**—Not an important factor. Circulation time variations are a matter of seconds and inconsequential. As maintenance proceeds an equilibrium tends to be established between agent dissolved in blood and that present in alveoli.

**Solubility in Tissues**—Adipose and other tissues of high lipid content have greater affinity for anesthetic than other tissues.

**Blood Supply to Tissues**—Tissues with abundant blood supply quickly come to equilibrium with agent dissolved in blood as follows.

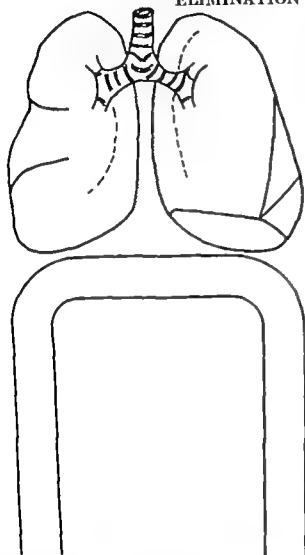
1. **Brain**—Contains considerable lipid and has excellent blood supply. Rapidly comes into equilibrium with blood and—narcosis ensues. Patient anesthetized before other tissues are saturated. Desaturation rapid.
2. **Adipose Tissues**—Possess poor blood supply. Cells contain up to 80% lipid material. Saturated readily. Desaturated slowly causing presence of agent particularly lipophilic agent in minute amounts in blood for many hours after administration is stopped.
3. **Muscles and Viscera**—Possess low lipid content but good blood supply. Quickly saturated with agents of low water solubility; cyclopropane, slowly saturated by agents of higher water solubility; equilibrium with blood established slowly. This type tissue acts as "buffer" and requires constant addition of agent to inhaled mixture during maintenance. Once saturation occurs desaturation is slow.
4. **Bone and Connective Tissue**—Lipoid content and blood supply poor. Saturation slow.





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**Blood Supply to Tissue**—Tissues with abundant blood supply quickly come to equilibrium with agent dissolved in blood as follows.

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## TECHNIQUES OF ADMINISTRATION OF VOLATILE AND GASEOUS ANESTHETICS BY INHALATION

### OPEN DROP TECHNIQUE

#### PRINCIPLE

A volatile liquid is evaporated on a flat, rigid layer of gauze which lies over on a wire mesh or similar suitable support. The vapors become mixed with air and are inhaled.

#### Advantages

1. Simple and unexplicated.
2. No appreciable dead space.
3. Air is diluent and the source of oxygen.
4. No resistance to inspiration or expiration.



#### Disadvantages

1. It becomes not really controlled unless it is added.
2.  $\text{CO}_2$  becomes not controllable may cause depletion (other).
3. Variations in rate of evaporation in relation to vapor which result in death.
4. Waste of anesthetic drug.
5. Fire hazard always present if dry.
6. Irritating concentrations often stimulate flow of serum or other.
7. Attainable concentrations of vapors for anesthesia due to rapid evaporation.
8. Liquid may irritate or burn skin.
9. Cold vapor reduces body temperature.

#### PRINCIPLE

Similar to the open mask except that mask is partly enclosed by two or similar device to obtain and increase concentrations of vapor.

#### Advantages

Same as open drop technique except that higher concentration of vapor more readily obtained. A necessity for adults or in hot climates.



### SEMI-OPEN TECHNIQUE

#### Disadvantages

1.  $\text{CO}_2$  retained by enclosure.
2. It becomes may be lowered to dangerous levels.

#### PRINCIPLE

Patient inhales through mask attached a reservoir (breathing bag) into which a mixture of gases and vapors of necessary composition flows directly. Exhalations pass outward through valve attached to a mask.

#### Advantages

1. Oxygen enriched mixtures may be used.
2. Fixed concentration of vapor because even plane of anesthesia.
3. Vapors and gases partly warmed.
4. Positive pressure may be used by closing valve.
5. Allows use of gaseous agents.
6. Low waste of vapors than by open method.



### SEMI-CLOSED TECHNIQUE

#### Disadvantages

1. Some accumulation of carbon dioxide.
2. Some rebreathing from mask and I.
3. Exhaled gas wasted, may be fire.
4. Flowmeter required in reservoir if.
5. Mechanical vapors required liquid agents.
6. Compressed gases required for use.
7. Complexity increased.

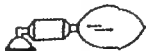
### CLOSED TECHNIQUE (WITH $\text{CO}_2$ ABSORPTION)

#### PRINCIPLE

Anesthetic vapors or gases are reabsorbed from an airtight closed tight fitting system.  $\text{CO}_2$  absorbed by alkali (soda lime). Constant stream of oxygen mixed with gases or vapors is supplied from flow meter.

#### Advantages

1. Resistance to expiration negligible.
2. A varying plane of anesthesia obtainable because of erratically maintained tension of drug.
3. Waste of drug is at minimum; economical.
4. Quiet and controllable respiration.
5. High humidity decreases fire hazard.
6. Vapors and gases are warmed.
7. Positive pressure may be employed.



#### Disadvantages

1. Alkaline dust from absorbent may.
2. Heat from reacting base may warm to undesirable temperature.
3. Tight fit necessary to obtain but often difficult to obtain.
4. Resistance to respiration may be as rates becomes defective.
5. Complexity sacrificed for comfort.
6. Dead space may be excessive in baby.
7. Flowmeter and compressed gases r

### INSUFFLATION

#### PRINCIPLE

A stream of gas or vapor combined with air or oxygen is directed into the mouth or nose of the patient.



not really controlled

## SECTION V GASEOUS AGENTS

### NITROUS OXIDE (NITROGEN MONOXIDE)

**HISTORY**—Prepared by Priestley in 1776. Anesthetic properties noted by Davy in 1799 in *Chemical Journal* but observation passed unnoticed. Cotton ( itinerant chemist and lecturer gave public demonstrations of it as "laughing gas" in early 1840's. In 1844 Horace Wells saw demonstration and used it clinically for dental work. Gave public demonstration for dental extraction in 1845. First used clinically with oxygen by Andrews in 1888 with positive pressure by Bert in 1880. Used as preliminary to ether (gas-ether) in 1876 by Clover.

**PREPARATION**—The commercial method employs ammonium nitrate which is heated to 240°C. The gas is collected, washed and compressed to a liquid which is stored in steel cylinders. The gas must be anhydrous.



**Solubility**—h at 37°C.

OS 14

OS 14



H<sub>2</sub>O 20



Blood 30

**Inflammability**—Not flammable when mixed with air or oxygen. Supports combustion and forms explosive mixtures when mixed with inflammable anesthetic gases and vapors even in absence of oxygen.

#### PROPERTIES

**Physical**—A colorless, inorganic gas possessing sweet taste and pleasant odor. Non-irritating. Molecular weight 44 specific gravity 1.53 (air equals 1). Converted to colorless liquid at 0° at 1,000 pounds pressure. Boiling point—88°. The gas is displaced as a liquid under 30 atmospheres pressure. Cylinders are marked blue for identification. Labeled in the U.S.P.

**Chemical**—Stable under pressure at ordinary temperatures. Forms nitric oxide when heated above 400°. Not inflammable but supports combustion even in absence of oxygen. Soluble in water and alcohol.

**Impurities**—Nitric oxide (NO) forms during manufacture; dangerous because it (1) combines with hemoglobin in same manner as carbon monoxide and causes asphyxia and (2) it combines with water to form nitric acid in the alveoli which damages alveoli and causes pulmonary edema. It impurities form at ordinary room temperature. Nitrogen decreases efficiency by dilution. Oxygen or carbon dioxide may become contaminant after manufacture or opening of package.

#### ADMINISTRATION

Anesthetic apparatus provided with source of pure oxygen, flow meters and closed or semi-closed inhalers are required. Positive pressure technique used to increase efficiency by increasing amount of drug in blood. May be given (inefficiently) by the gravity method (semi-open).

**Stability**—Inert—Not altered by soda lime or baralyme.

**Painful**—A mild anesthetic agent which rarely yields anesthesia below first phase. Not effective unless combined with narcotics or hypnotics such as morphine, veritru or other depressant drugs given as preanesthetic medication. Difficult to obtain surgical anesthesia without premedication or sub-oxygenation. Usually fortified with ether, chloroform, cyclopropane and other drugs. Anesthetic and analgesic action not due to hypnosis and obtained independent of it. Effects of anoxia are additive.

**Effects**—Concentrations of Inhaled Nitrous Oxide

Analgia 50 to 60% with air or oxygen; unconsciousness 85-90%, anesthesia 88-90% with oxygen. Rapid acting, usually 2-3 minutes. Twenty per cent yields analgesia equivalent to 10-15 mg. morphine.

**Margin of Safety**—Not lethal when administered with 60% or more oxygen (lethal (to animals) under three atmospheres pressure even when 60% oxygen is present. Danger lies entirely in anoxia often necessary to secure surgical anesthesia.

With Air

With Oxygen



**Elimination**—Not altered within the body. Major part eliminated through lungs unchanged within two minutes. Minute traces present in blood for several hours.

**Diffusion**—Passes rapidly through alveolar membranes. Collapse of isolated lung lobes with occluded bronchi and intact blood supply requires 17-23 minutes (air 10 hours). Minute amounts pass through skin during anesthesia.

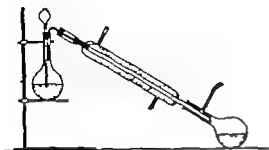






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**PREPARATION**—The commercial method employs ammonium nitrate which is heated to  $240^{\circ}\text{C}$ . The gas is collected, washed and compressed to a liquid which is stored in steel cylinders. The gas must be anhydrous.



#### PROPERTIES

**Physical**—A colorless, inorganic gas possessing sweet taste and pleasant odor. Non-irritating. Molecular weight 44; specific gravity 1.53 (air equals 1). Converted to a colorless liquid  $-10^{\circ}\text{C}$  at 1,000 pounds pressure. Boiling point  $-88^{\circ}\text{C}$ . The gas is dispersed as a liquid under 80 atmospheres pressure. Cylinders are marked blue for identification. Included in the U.S.P.

**Chemical**—Stable under pressure at ordinary temperatures. Forms nitric acid when heated above  $480^{\circ}\text{C}$ . Not inflammable but supports combustion even in absence of oxygen. Soluble in water and alcohol.

**In practice**—Nitric oxide (NO) forms during manufacture; dangerous because it (1) combines with hemoglobin in same manner as carbon monoxide and causes asphyxia and (2) it combines with water in form nitric acid in the alveoli which damages alveoli and causes pulmonary edema. No fumes form at ordinary room temperature. Nitrogen decreases efficiency by dilution. Oxygen or carbon dioxide may become contaminant after manufacture or opening of package.

**Solubility**—1. at  $5^{\circ}\text{C}$ .

Oil 1.4

Oil 1.4



H<sub>2</sub>O 44



Blood 47

**Inflammability**—Not inflammable when mixed with air or oxygen. Supports combustion and forms explosive mixtures when mixed with inflammable anesthetic gases and vapors even in absence of oxygen.

#### ADMINISTRATION

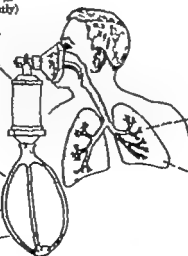
Anesthetic apparatus provided with a source of pure oxygen. Flow meters for closed or semi-closed inhalers are required. Positive pressure technique used to increase efficiency by increasing amount of drug in blood. May be given (inefficiently) by the gravity method (semi-open).

**Induction in a chamber**—Not altered by soda lime or baralyme.

**Potency**—A mild anesthetic agent which rarely yields anesthesia below first plane. Not efficient unless combined with narcotics or hypnotics such as morphine, veronal or other depressant drugs given as preliminary sedation. Difficult to obtain surgical anesthesia without premedication or subhypnotics. Locally fortified with ether, chloroform, cyclopropane and other drugs. Anesthetic and analgesic action not due to toxemia and obtained independent of it. Effects of agents are additive.

**Effective Concentrations of Inhaled Mixtures**—Analgesia 40 to 60% with air or oxygen, unconsciousness 55-75%, anesthesia 85-95% with oxygen. Rapid acting, usually 2-3 minutes. Twenty per cent yields analgesia equivalent to 10-15 mgm. morphine.

**Margin of Safety**—Not lethal when administered with 60% or more oxygen. Lethal (to animals) under three atmospheres pressure even when 80% air is present. Danger less entirely absorbed often necessary to secure surgical anesthesia.



With Air

With Oxygen



**Elimination**—Not altered within the body. Major part eliminated through lungs exhaled within two minutes. Minor traces present in blood for several hours.

**Diffusion**—Passes rapidly through alveolar membranes. Collapse of isolated lung lobules with occluded bronchioles and intact blood supply requires 17.55 minutes (air 18 hours). Minute amounts pass through skin during anesthesia.



**Blood Volume**—No significant change. Decreases if anoxia is present. Hemocoagulation results.

**Plasma Volume**—No significant change. Decreases if anoxia is present.

**Red Cells**—No increase in number; no increase in total hemoglobin; no change in fragility without anoxia. Drug more soluble in cells than in plasma. Number hemoglobin and cell volume percentage increases with anoxia due to constriction of spleen, decreased plasma volume and increased capillary permeability.

**Lymphocytes**—Polymorphonuclear cells doubled in number in first 18-24 hours and return to normal after 24 hours. Relative increase in lymphocytes, no change in morphology in any type cell.

**Platelets**—No increase in number or change in morphology or stability.

**Clothing Time**—No significant alteration. Prolonged clotting time may occur in the newborn.

**Bleeding Time**—Flight insignificant prolongation. Increase due to peripheral vasodilatation.

**Erythrocytes**—Increases with anoxia. Rapidly destroyed by enzymes of blood.

**Glucose**—Unchanged. Elevated with anoxia as a result of glycogenolysis.

**Lactic Acid**—Unchanged. Increased with anoxia from increased muscle spasms and disturbed carbohydrate metabolism.

**Concentration**—Solubility in plasma less than in water. Concentration varies widely but averages 65 volumes per cent. Concentration of plasma increases when administered under pressure. Most of gas disappears from blood within 3-5 minutes after discontinuing inhalation.

## URINE

No significant changes without anoxia.

## PATHOLOGY

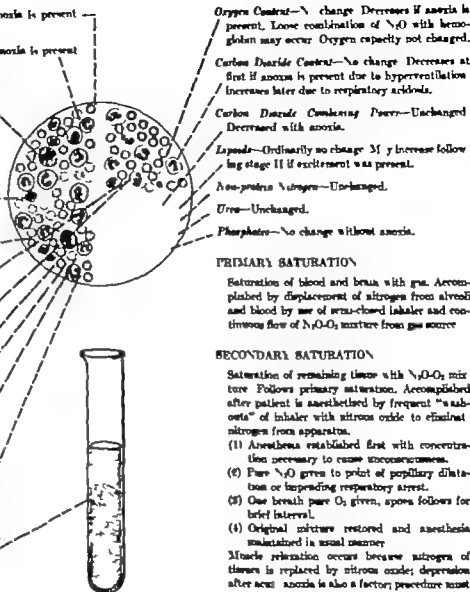
No specific gross or histo-pathological changes due to nitrous oxide itself occur. Changes due to anoxia are found in nervous and other tissues.

## USES

- (1) For major surgery in combination with basal narcotic drugs such as avertin, pentothal, morphine-acetaminophen et.
- (2) As pre-anesthetic or induction agent for ethyl ether or trichlorethylene.
- (3) For minor surgery which does not necessitate profound anesthesia.
- (4) For analgesia in dentistry and obstetrics.
- (5) When non-inflammable agents are required.

## CONTRAINDICATIONS

None provided no muscle relaxation is required and stage III is secured with no anoxia.



**Oxygen Content**—No change. Decreases if anoxia is present. Loose combination of  $\text{H}_2\text{O}$  with hemoglobin may occur. Oxygen capacity not changed.

**Carbon Dioxide Content**—No change. Decreases at first if anoxia is present due to hyperventilation. Increases later due to respiratory acidosis.

**Carbon Dioxide Combining Power**—Unchanged. Decreased with anoxia.

**Lipids**—Ordinarily no change. May increase following stage II if excitement was present.

**Non-protein Nitrogen**—Unchanged.

**Urea**—Unchanged.

**Phosphates**—No change without anoxia.

## PRIMARY SATURATION

Saturation of blood and brain with gas. Accomplished by displacement of nitrogen from alveoli and blood by use of semi-closed inhaler and continuous flow of  $\text{N}_2\text{O}-\text{O}_2$  mixture from gas source.

## SECONDARY SATURATION

Saturation of remaining tissue with  $\text{N}_2\text{O}-\text{O}_2$  mixture. Follows primary saturation. Accomplished after patient is anesthetized by frequent "suctions" of inhaler with nitrous oxide to eliminate nitrogen from apparatus.

- (1) Anesthesia established first with concentration necessary to cause unconsciousness.
- (2) Pure  $\text{N}_2\text{O}$  given to point of popliteal dilatation or impending respiratory arrest.
- (3) One breath pure  $\text{O}_2$  given, apnea follows for brief interval.
- (4) Original mixture restored and anesthesia maintained in usual manner.

Muscle relaxation occurs because nitrogen of tissues is replaced by nitrous oxide; depression after acute anoxia is also a factor; procedure must be repeated at varied intervals to maintain relaxation.

## ADVANTAGES

- (1) It is non-inflammable.
- (2) Non-irritating and pleasant to the patient.
- (3) Induction and recovery are rapid.
- (4) Has no deleterious action on circulatory, respiratory or other systems and organs.
- (5) It is an excellent general analgesic.
- (6) Inexpensive compared to many other drugs.
- (7) Post-anesthetic nausea and vomiting unusual.

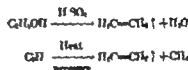
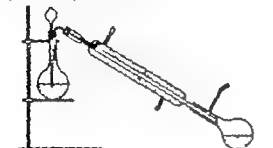
## DISADVANTAGES

- (1) Concentration necessary to produce stage III causes asphyxiation unless combined with a basal or some more potent agent.
- (2) Relaxation of muscles inadequate for general surgery.
- (3) Asphyxia is always a hazard.
- (4) Foam form of apparatus necessary for entering gases.

## ETHYLENE

**HISTORY**—Prepared by Bercher in 1680(?) Anesthetic properties first noted by Hermann in 1863 Crocker and Knight in 1908 noted toxicity to plants Luskhardt and Carter of Chicago introduced it in 1923 as an anesthetic for animals and man First clinical study by Isabella Herb 1924 in Chicago. Cotton in 1917 used ethylenated ether also investigated by W. E. Brown in 1924

**PREPARATION**—(1) The usual method of preparation is to dehydrate ethyl alcohol with sulphuric or phosphoric acid.  
(2) Also prepared by cracking propane. The gas is purified, liquefied and stored in steel cylinders.



## PROPERTIES



Ethylene is an unsaturated gaseous hydrocarbon. It is the simplest member of the alkene series.

**Physical**—A colorless non-toxic gas, possessing an ethereal odor and taste. Molecular weight 28 specific gravity 0.97 (air equals 1). Liquefies at  $-104^\circ\text{C}$  at 80 atmospheres pressure; boiling point  $-103^\circ\text{C}$ . Highly inflammable.

**Chemical**—Stable under ordinary circumstances, does not polymerize when stored under pressure in steel cylinders. Adds halogens to form organic halides and oxides to form oxides. Decolorizes solutions of potassium permanganate.

**Impurities**—Other hydrocarbons, such as acetone, propane, acetylene, carbon monoxide, phosphine, hydrogen sulphide, sulphur dioxide. May be contaminated with carbon dioxide, nitrogen or oxygen after manufacture. Most dangerous impurity is carbon monoxide. The solvent traces absorbed over a prolonged period during anesthesia cause asphyxiation by combining with hemoglobin.

**Properties**—Soluble but more potent than nitrous oxide. Flows freely under anesthesia below first phase. Muscle relaxation poor. Requires basal of morphine, atropine, pentothal or other depressant drugs to produce non-surgical surgical anesthesia. Effect of anoxia is additive. Ether, cyclopropane and other inhalation agents produce additive effects. May be used with curare to obtain muscle relaxation.

## ADMINISTRATION

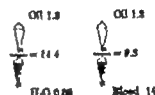
Apparatus equipped with flowmeter either vented or closed system is necessary. Closed methods safest because of fire hazard. A source of pure oxygen is necessary. Semi-closed method mandatory for induction to eliminate nitrogen.

**Effective Concentrations**—Amitane, 70-85%; nitrous oxide, 80%; oxygen, 15-20%. Induction rapid, requiring 1-2 minutes.

**Stability in Absorption**—Not altered by soda lime or baralyme or heat generated in container.

**Marginal Safety**—Not lethal unless embolization is present. Lethal at 70-80%  $\text{O}_2$  mixture to mice at 3 atmospheres pressure. Greatest hazards in clinical use are anoxia and inflammability.

Solubility  $\lambda$  at  $37^\circ\text{C}$ .



**Inflammability**—Flash point below  $56^\circ\text{F}$ ; 1 pound yields 482 cubic feet of inflammable mixture with air at  $68^\circ\text{F}$  at standard pressure. Minimum ignition temperature in air  $111^\circ\text{F}$  in oxygen,  $905^\circ\text{F}$ . Combustion supported by nitrous oxide. Insoluble and anesthetic concentrations are inflammable. Nitrogen and carbon dioxide act as quenching agents but are unstable because of anoxia or carbon dioxide excess.



**Elimination**—Not altered or combined in body with any tissue. Major portion eliminated in exhalation within two minutes. A lipophilic anesthetic which has great affinity for lipid tissues. Complete desaturation from fat deposits requires several hours. Minute traces detectable in blood ten hours after cessation of anesthesia.

**Diffusion**—Disappears from blood into tissues with blood supply. Exhaled and bronchus absorbed in 15-20 minutes (air—10 hours). Passes through skin 0.018 cubic cm per square cm per hour.



**Brain**—Cortex depressed. Cerebral cells irritated if anoxia is present causing convulsive phenomena which are softened by anesthesia

**Temperature Regulating Center**—Depressed in stage III thereby causing body temperature to vary with environmental temperature

**Vagus Center**—Not affected without anoxia.

**Cough Center**—Not affected.

**Vomiting Center**—Not affected. Nausea and emesis during recovery period if anoxia was present. Odor unpleasant if some patients may cause nausea.

**Pain Center**—Not affected. Stimulated if mild anoxia is present. Depressed during severe anoxia. Premedication masks previous effects.

**Respiratory Center**—Not affected. No respiratory depression unless anoxia is present and is severe

**Cerebral Body**—Not affected. Stimulated if anoxia is present and reflexly maintains respiration.

**Cerebral Spine**—Not affected. May reflexly elevate blood pressure with anoxia.

**Lungs**—Respiratory rate and amplitude not altered without anoxia. Alveolar and bronchial epithelium not irritated bronchial mucosa not affected. Bronchospasm uncommon. Increase in respiratory effort with anoxia causes hyperventilation which results in hypocapnia. Brief period of apnea follows removal of anoxic stimulus mediated by cerebral body until hypocapnia is overcome

**Musculature**—Oxygen consumption decreased in stage III.

**Diaphragm**—Movements not affected. Exaggerated with anoxia.

**Adrenal**—No evidence of significant changes chemically without anoxia. Depleted of epinephrine content with anoxia.

**Liver**—No significant effect. Reduction of power to convert d. l. folic acid. Glycogen depleted if anoxia is present

**Kidney**—No reduction in urinary volume. P.A.P. excretion not impaired

**Bladder**—Not affected

**Gonads**—Not affected

**Spleen**—Not relaxed.

**Intracranial Pressure**—Not affected. Increased with anoxia.

**Eyes**—No change. Eyeballs continue to oscillate. No effect on pupils dilat. with anoxia. Movements not affected. Corneal reflex remains active. Tear secretion not affected. Intraocular tension not significantly affected.

**Salivary Glands**—Not affected during induction depressed during maintenance not stimulated on recovery

**Pharynx**—Pharyngeal or "gag" reflex abolished; pharyngeal and nasal airways tolerated. Anoxia causes stertorous breathing due to spasm of muscles.

**Colon**—Activity decreased.

**Larynx**—Spasm uncommon. Non-irritating to mucous membranes. Cough reflex retained; intratracheal airways not tolerated. Laryngeal spasm with anoxia.

**Heart**—Rate normal or slightly increased. Coronary vessels, cardiac muscle and autonomic tissue not affected. No change in rhythm. Cardiac output not affected. Anoxia causes bradycardia and increase in irritability of autonomic tissue arrhythmias result. Severe anoxia causes depression of myocardium.

**Blood Pressure**—Not affected. Elevated with anoxia.

**Arterial Pressure**—No significant change. Elevated with anoxia.

**Spleen**—Not affected. Contracted with anoxia.

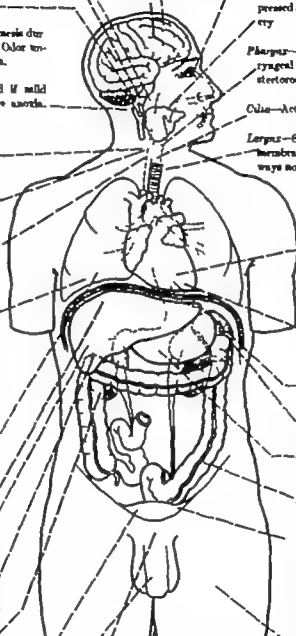
**Stomach**—Movements normal or slightly decreased. 7% increase in emptying time.

**Intestines**—Amplitude and frequency of movements maintained; tone not decreased.

**Uterus**—Amplitude and frequency of movements not significantly decreased. Drug passes through to fetus, but rapidly eliminated after delivery. Uterus not relaxed for intra-uterine manipulations. Anoxia of fetus results if less than 80% O<sub>2</sub> is used in inhaled mixture.

**Skeletal Muscles**—Small muscles partly relaxed; large muscles not relaxed. Twitching and spasticity if anoxia is present. Curare effective in combination with the gas. Does it itself possess a significant curare-like action.

**Skin**—Peripheral vessels dilated. Gas diffuses through skin; sweating absent unless anoxia is present. Ashes grey type of cyanosis appears with anoxia.



# THE PHARMACOLOGY OF ANESTHETIC DRUGS

**Total Blood Volume**—No significant change. Decreased with anaemia due to increase in respiratory permeability.

**Plasma Volume Percentage**—No significant change. Decreased with anaemia due to increase in respiratory permeability.

**Red Blood Cells**—No significant change in number or morphology. Fragility unchanged or slightly decreased. Hemoglobin content not changed. Red blood cells and hemoglobin increased with anaemia.

**Leucocytes**—Polymorphonuclears gradually increase in 1st 48 hours, return to normal within 48 hours. Increase is relative and absolute. No change in morphology.

**Platelets**—No change in number or stability.

**Oxygen Content**—No change without anaemia.

**Oxygen Capacity**—Unchanged.

**Carbon Dioxide Combining Power**—Increased for first 30 minutes (followed by a progressive decrease) without anaemia. Slight decrease and lowering of pH. Decreased with anaemia.

**Urea**—No significant change.

**Clotting Time**—No significant change clinically.

**Bleeding Time**—No significant change clinically.

**Glucose**—80% increase with return to normal in 24 hours. Prolonged elevation with increasing severity or duration of anaemia. Low content of liver.

**Lipids**—No significant change.

**Urea**—No change.

**Lactic Acid**—No change without anaemia.

**Ammonia Nitrogen**—No change.

**Phosphorus**—Decreases with return to normal within 48 hours.

**Concentration**—Arises rapidly. Average is 140 mgm. per 100 cc. 70% (80% of the drug is carried by the red cells, the remainder is in the plasma).

## PATHOLOGY

No gross or histopathological changes due to ethylurea itself occur. Changes due to anaemia as found in necrosis and other tissues.

## ADVANTAGES

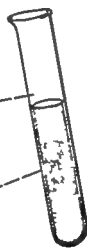
- (1) Non-irritating and pleasant to the patient.
- (2) Induction and recovery are rapid.
- (3) Has no deleterious action on circulatory, respiratory or other organs and organs.
- (4) Is an excellent general anaesthetic.
- (5) Inexpensive compared to many other drugs.
- (6) Post-anaesthetic nausea and vomiting unusual.
- (7) Somewhat more potent than nitrous oxide.

## DISADVANTAGES

- (1) Inflammable.
- (2) Older anaesthetics such as ether, chloroform, and nitrous oxide, are inhalers and are used.
- (3) Requires apparatus with flowmeters, an inhaler and gas.
- (4) Concentration necessary to produce stage III may cause apnoea without premedication.
- (5) Apnoea always a hazard.
- (6) Muscle relaxation, though greater than nitrous oxide, not sufficient for major surgery.

## CONTRAINDICATIONS

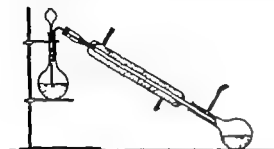
None provided no muscle relaxation is required and stage III is secured with no anaemia and no lightening source is present.



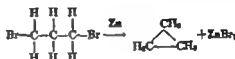
## CYCLOPROPANE

**HISTORY**—First prepared by the German chemist August von Freund in 1882. Anesthetic properties discovered on animals by V. E. Henderson and G. H. W. Lucas of Toronto in 1920. First clinical report by Ralph Waters in 1933 at the University of Wisconsin.

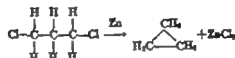
**PREPARATION**—(1) By treating 1,3-di-brom propane (Freund's method) with zinc (2) from 1,3-di-chlor propane (Haas). The ring is thereby completed.



(1)



(2)

Solubility  $\lambda$  at 37°C.

**Ignitability**—Highly flammable. Flash point below 0°C., 1 pound mixed with air yields 875 cubic feet of explosive mixture at 60°F and atmospheric pressure. Ignition temperature (minimum) 875°F in air 648°F in oxygen.

With Air



With Oxygen

With Air and  
Oxygen

## PROPERTIES

**Physical**—A colorless gas possessing a sweet odor and taste. Non-irritating. Molecular weight 42.08; specific gravity 1.46 (air equals 1). Liquefies at approximately 3 atmospheres pressure at room temperature; boiling point -34°C. Included in the U.S.P. XIII. 1 cu. vdp. equals 4.30 gals. Also known as trimethylene.

**Chemical**—A saturated cyclic hydrocarbon isomeric with propylene. Does not polymerize as stored under ordinary circumstances. Forms propylene at 100°C. with iron catalyst. Absorbed by sulphuric acid. Does not decolorize potassium permanganate solutions.

**Storage**—In steel alloy cylinders. Stable under ordinary conditions of storage.

**Purities**—Propylene, propane, allene, organic halides, cyclohexane may be present from manufacture. Inorganic gases such as nitrogen, carbon dioxide, and oxygen may contaminate after manufacture.

## Average Concentrations of Labeled Mixtures

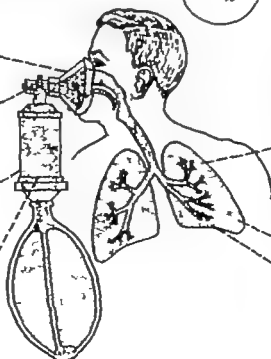
—Analogue 8 in 8% Unconsciousness  
4 to 8% Phase 1, 1 to 7% Phase 2, 7 to  
14% Phase 3, 14 to 25% Phase 4, 25 to  
40% (respiratory failure)

**Induction Time**—Rapid, 2 to 3 minutes.  
Possesses low solubility coefficient (air  
/blood ratio)

## ADMINISTRATION

By closed system only. Open or semi-  
open-closed too easily and hazardous.  
May be given by nasotracheal to infants—  
costly and hazardous.

**Stability in Absorber**—Not altered by alkali-  
line carbon dioxide absorbents.

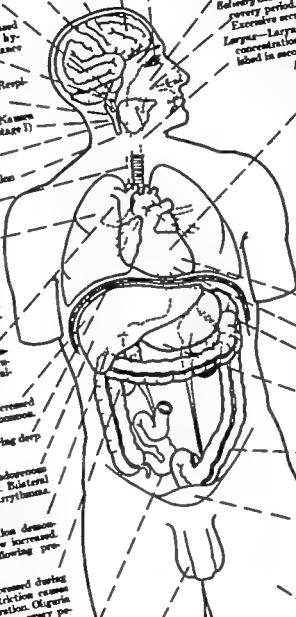


**Elimination**—Recovery with return of re-  
flexes occurs within 8 to 10 min. Not al-  
tered or combined in body. Major part  
eliminated in exhalations within 10 min.  
Complete desaturation requires several  
hours. Minute amounts detectable in  
blood for several hours after recovery.  
Minute amounts diffuse through the  
skin. Gas passes into gastrointestinal  
tract, air collections in pleura and other  
hollow viscera.

**Diffusion**—Rapid from isolated lung lob-  
ule. Passes through rubber.

**Effect on Tissues**—No histological changes  
characteristic of drug occurs in any or-  
gan, including heart.





**Blood**—Total volume reduced. Cell volume increased.

**Red Blood Cells**—Slight increase in number. Fragility not changed. Slight increase in hemoglobin. Two and one-half times more drug in red cells than in plasma.

**Leukocytes**—No significant changes during anesthesia. Increased 10- or 150 times after withdrawal maximum in 8 hours returns to normal in 48 hours. Polymorphonuclear cells increase relatively and absolutely.

**Platelets**—No significant changes in number.

**Oxygen Content**—Arterial blood 100% saturated. Venous oxygen increases and tends to become arterIALIZED.

**Carbon Dioxide**—Total carbon dioxide content increased. Carbon dioxide tension increased result big in metabolic acidosis. (May affect vasomotor center and arterioles.)

**Carbon Dioxide Combining Power**—No significant alteration. Decreased 5-7%. No significant changes even in diabetic patients.

**Clotting Time**—Unchanged. Apparent increased bleeding due to dilatation of peripheral vessels and elevation in blood pressure. Hemostasis in surgical wounds no more frequent than with other agents.

**Reclotting Time**—Unchanged.

**Prothrombin Time**—Unchanged.

**Urine**—Decreased volume and output during anesthesia; increased after anesthesia.

**Phosphorus**—No change. Increased for several hours after anesthesia, then returns to normal.

**Van-protein Nitrogen**—Increased during and returns to normal after anesthesia.

#### CLINICAL USES

- (1) For all types of major surgery requiring relaxation of large muscles.
- (2) As rapid inducing agent for ether or other types of anesthesia.
- (3) As supplemental agent following rectal, intravenous and regional anesthetics.
- (4) For thoracic surgery and for diseases of the respiratory system.
- (5) For patients in shock from trauma or hemorrhage.
- (6) For patients who have severe metabolic disturbances (diabetes, nephritis, hepatitis, etc.).
- (7) When light anesthesia is desired (with ether).

#### ADVANTAGES

- (1) Possesses wide margins of safety.
- (2) Induces anesthesia in all planes.
- (3) Induction is pleasant and rapid.
- (4) Salivation or laryngeal secretions are absent.
- (5) Respiration is quiet, diaphragmatic movements not exaggerated.
- (6) Lethal—allows immediate hyperventilation and deepening of anesthesia.
- (7) Apnea is easily induced, facilitating controlled respiration when desired.
- (8) Does not shut out metabolic processes and blood chemical patterns significantly.
- (9) Recovery is rapid.

**Plasma**—Hemoconcentration. Volume reduced.

**Total Base**—May increase slightly. No significant change ordinarily.

**Sedum**—May decrease slightly.

**Polysolium**—Decreased in plasma.

**Inorganic Phosphorus**—Unchanged.

**Glucose**—Increased an average of 8 to 30 mgm. per 100 cc.

**Van-protein Nitrogen**—Decreased after anesthesia. Uric acid excretion increased. Changes not clinically significant.

**Lactic Acid**—Increases slightly. Not clinically significant.

**Urine**—Increased during and returned to normal after anesthesia. Not clinically significant.

**Drug Concentration**—8 to 15 mgm. average during 1st to 2nd plane. Anesthesia 16-20 mgm. per 100 cc. for second to third plane anesthesia. Concentration in venous blood equals arterial blood 15 minutes after induction. Concentration in fetal blood equals maternal blood after 15 minutes of anesthesia.



#### CONTRAINDICATIONS

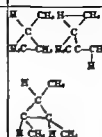

- (1) The presence of cardiac disease or irregularities of rhythm.
- (2) The simultaneous use of epinephrine and related drugs.
- (3) The use of cauteries or electrical equipment during surgery.

#### DISADVANTAGES

- (1) Considerably more expensive than other gases.
- (2) Forms highly explosive mixtures with air or oxygen in anesthetic concentrations.
- (3) Increases irritability of cardiac autonomic tissue predisposing to arrhythmias.
- (4) Adequate muscle relaxation not obtained consistently.
- (5) Hoarse and capillary bleeding frequently encountered.
- (6) Hypertension often encountered.
- (7) Laryngeal spasm during induction and recovery common.
- (8) Emergence delirium frequent during recovery.
- (9) Post anesthetic nausea occurs frequently.
- (10) Respiratory depression and troublesome apnea common.
- (11) Post anesthetic hypotension (hypotensive shock) often observed in long operations.
- (12) Carbon dioxide tension increased, causing metabolic acidosis.




## LESSER KNOWN HYDROCARBONS

[illegible]

	Beta Butylene	Isoprene	Acetylene	Allylene	Butadiene	Acetylene	Methyl Cyclopropane	Cyclobutene
History	Schmidt and Schenck studied it in 1903.	Kilham studied it on rabbits.	Investigated by Bauer 1937	Schmidt and Schenck studied its effects.	Studied by Walland, Kneve as Allylene. Lighter than air 2.0 g/l. Oil water ratio 5.5 at 30°C.	Studied by Walland, Kneve as Allylene. Lighter than air 2.0 g/l. Oil water ratio 5.5 at 30°C.	Henderson studied these effects in animals in 1937	Prepared and studied by Kruetz in 1946.
Chemical structure	CH <sub>2</sub> =CH-CH=CH <sub>2</sub>	CH <sub>2</sub> =C(CH <sub>3</sub> )=CH-CH <sub>3</sub>	CH <sub>2</sub> =C(CH <sub>3</sub> )=C(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> =C=CH <sub>2</sub>	CH <sub>2</sub> =CH-CH=CH <sub>2</sub>	HC≡CH	Cyclic hydrocarbon.	
Chemical formula	CH <sub>2</sub> =CH-CH=CH <sub>2</sub>	CH <sub>2</sub> =C(CH <sub>3</sub> )=CH-CH <sub>3</sub>	CH <sub>2</sub> =C(CH <sub>3</sub> )=C(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> =C=CH <sub>2</sub>	CH <sub>2</sub> =CH-CH=CH <sub>2</sub>	HC≡CH		
Properties	Explosive mixture in air, B.P. 1.5°C. M.W. 54. Oil water ratio 19.5. Also known as isobutylene.	B.P. -5°C. M.W. 66. Colorless liquid. Boils at 22-26°C. Insoluble. Polymerizes to higher molecular weight hydrocarbons.	A diatomic. Colorless gas with odor like propylene. Insoluble. Oil water ratio 107.5. B.P. -85.5°F. M.W. 26. Oil water ratio 97 at 30°C. Polymerizes in storage.	A diatomic. Colorless gas with odor like propylene. Insoluble. Oil water ratio 107.5. B.P. -85.5°F. M.W. 26. Oil water ratio 97 at 30°C. Polymerizes in storage.	Colorless gas with disagreeable odor and taste after taste. Explosive spontaneously at 17°C. Insoluble in water. Formed in cylinders containing solvents sealed with acetone.	Colorless gas with disagreeable odor and taste after taste. Explosive spontaneously at 17°C. Insoluble in water. Formed in cylinders containing solvents sealed with acetone.	Colorless gas. (see methyl cyclopropane)	Colorless gas possessing odor like cyclopropane. Insoluble in water. Soluble in ether. Soluble in oil.
Toxicity	More potent than propylene. Potency increases almost in proportion to M.W. increases.	More potent than propylene.	More potent than propylene or butadiene.	More potent than propylene.	More potent than allylene.	Slightly more potent than allylene.	More potent than cyclopropane (all three). Potency increases with M.W. of each agent.	More potent than cyclopropane.
Inflammability	5-15% in air.	5-15% in air 5-45% in oxygen.	Inflammable.	Inflammable.	Inflammable.	5.5-40% in air 5.5-45% in oxygen.	Inflammable.	Inflammable.
Concentration for anesthesia	50-60% yields anesthesia. 70% lethal.	50-65% yields anesthesia.	6% yields anesthesia.	6% gives to anesthesia maximum 60% lethal.	10-15% for anesthesia. Narrow margin of safety.	Anesthesia 50-60%. First phase 60-75%. Second phase 70-85%.	15% mono-anesthetic, 10% di-anesthetic, 5% tri-anesthetic. 50-60% required for induction. Induction and recovery rapid.	
Absorption and elimination	Rapidly absorbed through lungs.	Rapidly absorbed through lungs.	Rapidly absorbed through lungs.	Rapidly absorbed through lungs.	Through the lungs unchanged.	Rapidly absorbed. Induction appears 5-10 sec. Fully absorbed in 1-2 min. Eliminated unchanged—65% in exhalation.	Presumably eliminated unchanged through lungs.	Through lungs probably unchanged.
Circulatory effects	Arrhythmias and deceleration of cardiac subsidiary action.	Arrhythmias, tachycardias and L.S. in blood pressure common.	Arrhythmias frequent.	Pulse rate increases. Blood pressure elevated.	Tachycardias, arrhythmias and increases in blood pressure.	Common to the blood pressure. Vasoconstrictor effect. Pulse elevated. Respiratory volume increases.	Increased search for tachycardias, deceleration of cardiac subsidiary action.	Somewhat like cyclopropane. Sometimes heart is stimulated causing tachycardia.
Respiratory effects	Causes hyperpnea and pulmonary irritation.	Causes hyperpnea and pulmonary irritation.		Rate and depth increased.	Causes marked hyperpnea.	Respiration does not fall unless anxiety is present. Does not yield anesthesia deeper than third phase. Non-irritating.		Similar to cyclopropane.
Metabolic and other effects			Not studied.			Does not depress (lower) arterial CO <sub>2</sub> tension. Power. Some elevation in blood sugar. No effect on milk.		Similar to cyclopropane.
Method of administration	Closed system with oxygen.	Closed system with oxygen.	Inhalation or intravenously.	By inhalation.	By inhalation.	Closed or semi-closed system. Anesthesia may be achieved by washing or absorption with charcoal.	Administered by inhalation.	By inhalation in closed system.
Conclusions	Not clinically useful.	Not clinically useful.	Not clinically useful.	Not clinically useful.	Not clinically useful.	Does not yield satisfactory anesthetic relaxation. Animals may recover from same respiratory failure without anesthetic output.	Not useful clinically.	Has been used in man. Relieves like cyclopropane.

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

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Name	Cyclopropane	Cyclohexane	Spiropentane	Isomers	Sulphur hexafluoride
History	Studied by Virtue 1919	Studied by Virtue 1939	Studied by Soumers 1939	Mixture of hydrocarbons from petroleum 175°-415°C fraction.	Studied by Virtue as Weaver 1942.
Chemical structure	Saturated cyclic hydrocarbon.	Hexa-hydrobenzene from petroleum.	A hexane cyclic hydrocarbon 2 cyclopropanes.	—	Sulphur with six fluorine atoms. Very stable.
					BP
Properties	Mobile, clear liquid, B.P. 34.2°C. S.G. 0.749 at 60° Refract. 1.408 at 20°	Mobile clear liquid, B.P. 80.8°C. S.G. 0.7781 at 20°C.	Mobile liquid B.P. 59.03 Refract. 1.4192 at 20°	Chlorides and aromatics removed	Gasous agent. Inert, stable, highly insoluble in water 8.1%—Ea 9.97
Potency	Seven times more than cyclopropane (07 versus .005 mole)	Cyclopropane (07 versus 018 mole)	More potent than cyclopropane	Varies with source	Low potency than nitrous oxide. Probably does not have water solubility
Inflammability	Flammable	1.5%—3.4% by vol in air Flash Point 88°	Flammable	Flammable	Not flammable.
Concentration	9% anesthetic index 1.44.	3-6% anesthetic index 1.92.	2-9% since 7% resp failure.	Absorbed slowly from blood. Eliminated slowly Requires days.	75%—81% O <sub>2</sub> Very inert.
Absorption and elimination	By inhalation. Presumably unchanged in body	By inhalation.	Induction 3-5 min. Recovery 2-10 minutes.	Depresses heart. Pulmonary edema results.	By inhalation with a gas.
Circulatory effect	Arrhythmias, "sensitive heart" epinephrine	Similar to cyclopropane, but more toxic	B.P. falls. Tachycardia, myocardial depression	Toxic to liver kidney	N. remarkable effect
Metabolic effects	Not studied Causes twitching and convulsive movements.			Not used Accidental poisoning	By inhalation
Method of administration	Volatilized. Vapor inhaled.	By inhalation.	By inhalation with oxygen.	Depression of C.N.S. occurs, also pulmonary edema.	Not potent used alone. Not clinically useful. Not effective in animals.
Uses/abuses	Toxic manifest those limit clinical usefulness.	Not clinically useful. Produces neurovascular manifestations.	Not clinically useful. Produces convulsive manifestations.		

# SECTION VI. VOLATILE AGENTS

## ETHYL ETHER

**HISTORY**—Synthesis described by Valerius Cordus (Germany) in 1540 who called it "sweet vitriol." Paracelsus (Switzerland) in 1540 mentioned pain relieving qualities. Named "ether" by Frobenius (Germany) in 1703. Richard Pearson (England) in 1794 used inhalations for treatment of phthisis. Report of deep sleep induced by ether reported by Beddoes in 1794. Michael Faraday in 1818 recorded stupefying effects of the compound. W. F. Clark (U. S.) in 1842 administered it in extraction of a tooth. Used clinically several months later by Crawford W. Long in 1842 after having experience with "ether frolics" in Athens, Georgia. In 1803 John C. Warren (U. S.) used ether to relieve last stages of pulmonary inflammation. Charles T. Jackson (U. S.) in 1816 suggested its use to Morton who removed a tooth successfully with it. First public demonstration by William T. G. Morton in 1846 in Boston. Used as a surgical anesthetic by Morton for removal of tumor of jaw by Dr. J. C. Warren in 1846. John Snow in 1847 was first physician anesthetist to use ether at St. George's hospital, London. Originally called "letheen" by Morton.

**PREPARATION**—Most common method is to dehydrate ethyl alcohol with sulphuric acid below 140°C.



### PROPERTIES

**Physical**—A colorless, highly volatile liquid possessing pungent odor and yielding no limited vapour. Molecular weight 74. Specific gravity 0.718 at 15°C. Boiling point 34.5°C. Specific gravity of vapour 2.6 (air equals 1). U.S.P. preparation contains alcohol (up to 3.5%).

**Chemical**—Does not react with alkalis. Reacts with sulphuric acid to form ethyl sulphate; with hydrochloric acid to form alcohol and ethyl chloride.

**Impurities of Manufacture**—Alcohol, mercaptans, sulphuric acid, sulphur dioxide, ethyl esters, sulphurous acid, acetaldehyde and other peroxide.

**Impurities of Decomposition**—Form ethyl peroxides  $[(C_2H_5)_2O_2]$  which act on the alcohol to form acetaldehyde. Oxidation of ether is favored by air, moisture and light, retarded by copper, iron, mercury and zinc but not the organic acids (form later from aldehydes). Impurities prolong induction period. Not fatally toxic. Peroxides are unstable; may cause spontaneous combustion and contribute to explosion hazard.

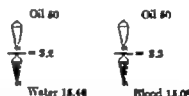
**Storage**—Kept in metal containers coated inside with copper, iron or other metal which combines with oxygen, oxidation thereby retarded due to preferential absorption of oxygen by the metal. Oxidation rapidly in open containers, in air or when heated in the presence of oxygen.

**Stability as Anesthetic**—Not altered by soda, lime or barium-lime structures.

**Concentration**—For anaesthesia less than 1% by volume in inhaled mixture. For anaesthesia average 3.5% to 4.5% by volume. T. rises respiratory failure 6.7% to 8%. Higher concentrations necessary during induction; it is not used quickly. Possesses wide margin of safety. Respiratory failure precedes circulatory failure. Probability of resuscitation good in event of respiratory failure.

**Induction**—Prolonged, particularly second stage. Due to irritating qualities, high air blood ratio and moderate solubility in all tissues. Water solubility greater than is true with other common inhalation anesthetic agents.

**Solubility**—A at 37°C.



**Inflammability**—Flash point below 34°F. Ignition temperature 301° in air; in oxygen 339°C. 1 pound with air gives 677 cubic feet of inflammable mixture at 60°F at standard pressure.

With Air



With Oxygen



With Vapour



**Elimination**—Not altered within the body; 85% to 90% of a given dose is eliminated through lungs; remainder through skin, urine or with other body fluids. Rate of desaturation depends upon depth and duration of anaesthesia, amount of Epikid tissue and blood supply to tissues. Desaturation is slow, requiring many hours. Flow desaturation result of high blood solubility coefficient and moderate degree of solubility in "watery" tissues.

**Distribution**—Passes rapidly through alveolar membranes. Differs from isolated lung isolate intact in 1 to 3 minutes (air—18 hours).



**Lungs**—Absorption increased through peritoneal cavity particularly diaphragmatic portion. Enhanced by increased respiratory activity. Parent material in peritonitis may be rapidly absorbed.

**Adrenal**—Sympathetic stimulation causes depletion of epinephrine content of gland.

**Liver**—Function decreased (Bromsulphalein dye test) returns to normal in 24 hours. Bile secretion decreased. Activity of reticulo-endothelial cells depressed. Glycogen content decreased rapidly (80%) in first hour then gradually decreased. Urea formation unaffected. No histological changes characteristic of drug.

**Kidney**—Oliguria in stage III, possibly due to release of anti-diuretic hormone from pituitary. Compensatory polyuria follows during recovery. Renal function further impaired in nephritis, sepsis or other renal insufficiencies. No histological changes characteristic of drug.

**Uterus**—Stimulation of contractions during light anesthesia.

**Bladder**—Contracts at onset of stage III. Stretch reflex disappears causing stony of bladder and urinary retention. Reflexes may cease slowly to persist in post-anesthetic period.

**Gonads**—No significant effects. Cholesterol content of testes reduced.

**Body Temperature**—Decreased due to decreased metabolic rate depression of temperature regulating center and heat loss through skin due to dilatation of vessels.

**Skin**—Temperature increased due to dilatation of peripheral vessels. Forming common particularly with anoxia or in warm environment. Blistering and burns may occur from local application under pressure.

**Spleen**—Constricted if structure is normal blood flow unchanged. Causes erythrocytes to pass into systemic circulation.

**Stomach**—Swallowed vapors cause vomiting by irritation of mucous membranes. Movements decreased; emptying time decreased 50%. Gastric secretion decreased acidity decreased. Muscle relaxed, causing dilatation 15 minutes to 1 hour after anesthesia.

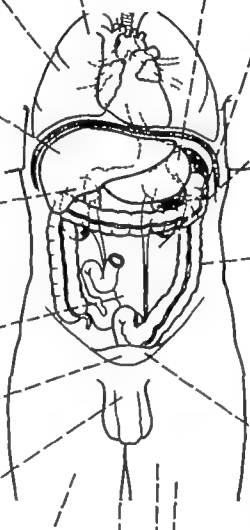
**Pancreas**—Insulin production decreased. Blood amylase increased 75-100%. Prevents or inhibits the action of insulin.

**Intestines**—Decreased peristalsis and secretions due to sympathetic stimulation and smooth muscle depression. Vessels dilated with loss of muscle tone. Peristalsis exaggerated on recovery. Mobility remains abnormal up to 48 hours. Colon becomes spastic 4 or 5 hours after recovery causing gas to accumulate in small bowel and cramps in post-operative period.

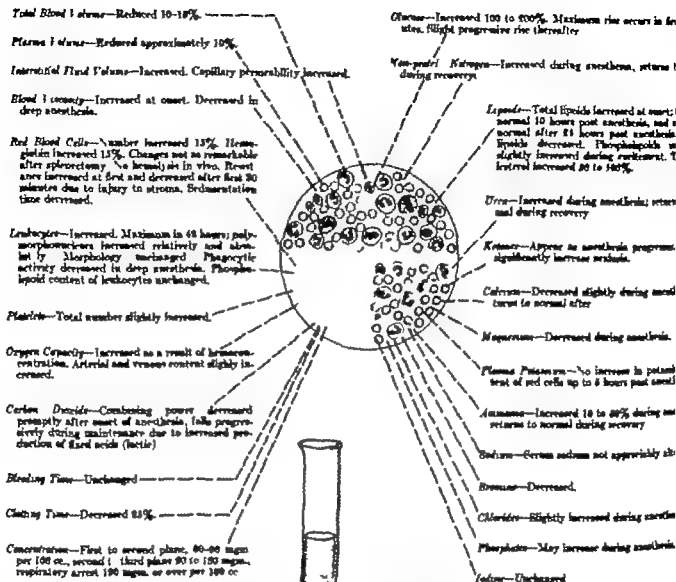
**Uterus**—Movements decreased. Intra-uterine pressure decreased. Relaxation complete in deep anesthesia. Drug passes through placenta. Arterial oxygen normal in fetus.

**Muscles**—Relaxation of skeletal muscles satisfactory. Glycogen content partly reduced. Lactic acid increased. Possesses curare-like action at end plates. Marked additive action with curare and tubocurarine.

**Peripheral Nerves**—Direct excitability not affected when central nervous system is depressed. Direct application depresses activity and conduction.







## URINE

Output decreased during anesthesia. Phosphates increased up to 500%, albumin present in 80% of cases post anesthesia. Ketones appear after anesthesia has been maintained for some time or post-operatively. Nitrogen output increased after anesthesia for 4 hours; decreased during anesthesia.

## USES

1. For all types of surgery, particularly when relaxation of muscles is required.
2. For an additive effect with mildly potent agents.
3. As a complementing agent to basal anesthetic obtained with avertin, barbiturates and other non-volatile agents.
4. As an analgesic (rectally).
5. As an antispasmodic for rectal or intravenous use.

## CONTRAINDICATIONS

1. Presence of acute respiratory infection.
2. Presence of chronic respiratory infection.
3. Acidosis from any cause.
4. Presence of severe hepatic or renal insufficiency or injury.
5. Surgery requiring use of cautery.
6. Shock from trauma or hemorrhage.
7. History of convulsions in previous anesthetics.

## DISADVANTAGES

1. Period of induction prolonged, unpleasant and often occurs by excitement.
2. Recovery is slow (saturation and de-saturation requires considerable time).
3. Inflammable.
4. Irritating to respiratory passages, causing excessive salivation, nose secretion and spasm.
5. Disturbs important metabolic functions.
6. Nausea and vomiting frequent post-operatively.
7. Convulsions may occur in rare cases.

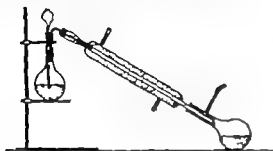
## ADVANTAGES

1. It is sufficiently potent for all forms of major surgery.
2. It possesses a wide margin of safety.
3. It is not a circulatory depressant at level of anesthesia usually employed for surgery.
4. It tends to stimulate respiratory movements at level of onset used for surgery.
5. It is stable and readily preserved.
6. It is relatively inexpensive.
7. May be administered with a minimum of equipment if person concentration required for anesthesia is low.
8. Safest of the volatile agents in the hands of inexperienced handlers.

## DIVINYLOXIDE (VINETHIENE)

**HISTORY**—Apparently first prepared by F. W. Semmler in 1887 in Germany. First successful synthesis by William Rugh in 1931. Anesthetic properties described by Chauncey Leake and M. Y. Chen in 1930 in United States. Further reports by Goldschmidt and Ravdin in 1933.

**PREPARATION**—Fusion of BB dichloro-ether with potassium hydroxide with ammonia as catalyst.



## PROPERTIES

**Physical**—Highly volatile, clear limpid fluid, possessing an ethereal, non-pungent odor which yields a non-irritating vapor. Molecular weight 70 specific gravity 0.77 at 20°C.; boiling point 23.5°C. vapor specific gravity 2.8 (air equals 1).

**Chemical**—Unstable; decomposed by light, heat, air. Forms various peroxides, formaldehyde and acrolein aldehyde which polymerize to resins. Also forms formic acid and acetic acid. Decomposition inhibited by ammonia and amines. Also known as vinyl oxide divinyl ether vinethene.

**Impurities of Manufacture**—Aldehydes, chloroethers, diisobutylene oxide, acrolein and formic acids and peroxides.

**Storage**—In dark, tightly-sealed bottle with an amine as an i-catalyst (Merck's "Vinethene" contains divinyl oxide 4% ethylene alcohol to prevent freezing of exhaled water vapor on mask, and 0.1% phenyl-alpha-naphthylamine which acts as a stabilizer in preventing polymerization). **Shelf-life**: container fluorescent thimble to product. Opened bottle should be discarded 10 days. Decomposes slowly (its parent) in container. Should be discarded after date of expiration on label.

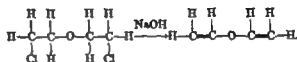
## ADMINISTRATION

Open, semi-open or closed techniques may be used. Even anesthesia best obtained by open drop method. May be combined with nitrous oxide in semi-closed system.

**Induction**—Rapid. Unconsciousness occurs in one or two minutes. Pleasant without excitement.

**Effectful Inspired Concentrations**—Analgesia, approximately 0.5%; unconsciousness 2 to 4%. Anesthesia 4%; respiratory arrest 10 to 12%.

**Stability in Absorber**—Not altered by alkaline carbon dioxide absorbents.



Solubility at 27.5°C.



0.28 gm per liter H<sub>2</sub>O

**Inflammability**—Highly explosive when vaporized with air or oxygen. Flash point below 94°F. One pound with air yields 819 cubic feet of explosive mixture at 60°F. and at atmospheric pressure. Ignition temperature 660° in air; 661° in oxygen.

With Air

1.70%

87.0%

With Oxygen

1.88%

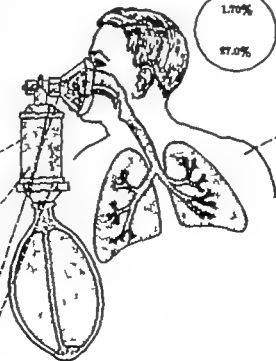
85.8%

With Nitrous Oxide

1.40%

81.8%

**Elimination**—Not altered in the body. Major part eliminated through lungs. Recovery occurs in three to five minutes. Small amount eliminated through skin and other body excretions. Major portion eliminated within short period. Complete body destruction slow because drug is lipophilic. Post anesthetic somnolence does not occur.



# THE PHARMACOLOGY OF ANESTHETIC DRUGS

**Cortex**—Depressed. All planes of anesthesia obtained. Convulsions may occur from stimulation of central nervous system (subcortical centers).  
 Maintained or prevented by premedication with morphine.

**Forming Center**—Not stimulated. Hiccups not common during recovery.

**Respiratory Center**—Depressed only in phase 4. Respiration fails before circulation.

**Vasomotor Center**—No appreciable effect during surgical anesthetic.

**Lungs**—Non-irritating to epithelial lining.  
 At onset respirations rapid and shallow; respiration ceases before circulation fails. Minute volume exchange increased at onset and in light anesthesia; decreased in deeper planes.

**Bronchi**—Dilated. Bronchospasm uncommon.

**Metabolism**—Oxygen consumption increased at onset due to increased muscle activity; decreased during maintenance.

**Diaphragm**—Movements not exaggerated.

**Adrenal**—Epinephrine content not changed. Drug behaves in same respect as sympathomimetic substance.

**Gallbladder**—Bile secretion decreased in amount with return to normal or an increase after anesthesia.

**Liver**—Bile excretion not impaired. Central necrosis and decreased liver function with anoxia on prolonged or repeated use. Drug contraindicated in liver disease.

**Kidney**—No evidence of impaired function after brief periods of use. Impaired urea clearance after prolonged or repeated use.

**Sphincters**—Relaxed in lower planes of anesthesia.

**Intracranial Pressure**—No remarkable or significant change. Anesthetic headache may follow.

**Eyes**—Lid reflex disappears in first plane. Pupillary reflex to light remains active. Horizontal nystagmus, eyeballs rotate away in third plane anesthesia. Movements not reliable for judging anesthesia. Judge depth of respiration not eye signs.

**Salivary Glands**—Frequently copious secretions during induction period. Controlled by atropine.

**Pharynx**—"Gag" reflex abolished. Mucous glands stimulated. No laryngeal spasm. Occasionally causes excessive secretion of mucus.

**Larynx**—Laryngeal reflex abolished. Deep anesthesia. Spasm and phon may occur from excessive mucus.

**Heart**—No notable cardiac effect. Slightly increased or decreased. EKG not changed. No effect on automaticity. Arrhythmias uncommon. Does not sensitize heart to curare.

**Blood Pressure**—Not changed or decreased in deep anesthesia.

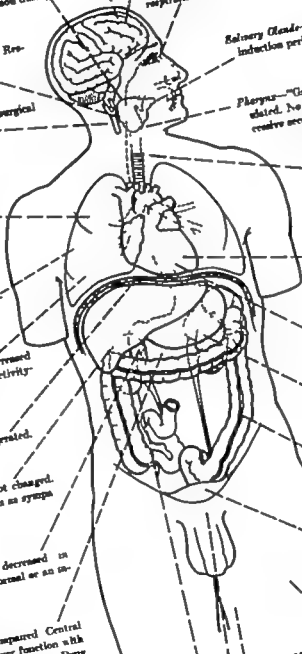
**Stomach**—Gastric tone increased. Emptying time decreased 75%.

**Intestine**—Decreased muscular tone of small bowel. Movements inhibited in vivo decreased in deep anesthesia. Data on effect on colon lacking.

**Uterus**—Frequency of contractions not affected in light anesthesia, and usually drug passes to fetus.

**Skeletal Muscles**—Relaxation of abdominal muscles not reliable. Iliopsoas muscles of extremities relaxed for whole surgery.

**Skin**—Sweating minimal. N. cyanosis. Possibility of burns in pressure and direct contact of agent on cutaneous areas.



**BLOOD**

Oxygen Capacity—Unchanged.

Oxygen Content—Unchanged in arterial system.

Carbon Dioxide Combining Power—Slightly elevated or unchanged.

**PATHOLOGY**

Central necrosis of liver lobule in animal experiments in prolonged anesthesia or when administered with anoxia. No definite evidence of any similar effect on man.

**URINE**

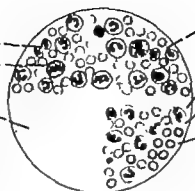
No significant changes. Urea clearance impaired in prolonged anesthesia or in repeated administrations.

**USES**

- (1) For analgesia for minor operations (excisions, obstetrics, etc.) of short duration (less than 10 minutes)
- (2) For anesthesia for brief surgical procedures not requiring relaxation.
- (3) As a pre-anesthetic in open drop ether anesthesia to shorten second stage
- (4) As complement to nitrous oxide or ethylene anesthesia.
- (4) In combination with ethyl ether

**DISADVANTAGES**

- (1) Relatively expensive (compared to ether)
- (2) Inflammable
- (3) Not as stable chemically as other volatile agents.
- (4) Possibility of convulsions, particularly in unpremedicated subjects
- (4) Muscle relaxation unsatisfactory
- (6)  $F_2$  signs not reliable guide to anesthesia.
- (7) Possibility of hepatic or renal damage in repeated prolonged use
- (8) Excess salivation occasionally encountered.
- (9) Odor objectionable at first.
- (10) Post-anesthetic headache occasionally seen.
- (11) Highly volatile at room temperature
- (12) Chances of resuscitation less than with ether in event of overdosage
- (13) Not satisfactory in closed system



Glucose—Unchanged.

Clotting Time—Unchanged.

Bleeding Time—Unchanged.

Blood Concentration—Average 11 mgm. per 100 cc. for 1st plane; average 16 mgm. for 2nd plane; 28 for 3rd plane and 68 mgm. for respiratory failure.

**CONVULSIONS****Features**

- (1) Occur during induction.
- (2) Occur in unpremedicated subjects.
- (3) Due to stimulation of spinal and subcortical motor centers.
- (4) Disappear when agent is discontinued.

**CONTRAINDICATIONS**

- (1) Operations requiring muscle relaxation
- (2) Operations lasting more than 18–20 minutes.
- (3) The presence of hepatic, renal disease or tendency to "convulsive states."
- (4) The presence of anoxia.
- (5) The presence of cavity or other source of ignition.

**ADVANTAGES**

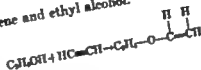
- (1) Rapid, pleasant induction.
- (2) Rapid recovery
- (3) Excitement rare
- (4) Non-irritating to respiratory tract.
- (5) Nausea and vomiting uncommon.
- (6) Minimal equipment necessary for administration.
- (7) Does not depress respiration.
- (8) Does not affect circulation.
- (9) May be inhaled directly without unpleasantness, spasm or coughing.
- (10) Respiration ceases before circulation in overdosage
- (11) Yields all planes of anesthesia.
- (12) May be combined with ether or nitrous oxide
- (13) Does not notably interfere with important physiological functions.
- (14) Useful for emergency room surgery

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

## VINYL ETHYL ETHER (VINAMAR)

**HISTORY**—First studied by Leake in 4 mice (U.S.) in 1930 who obtained specimen from Fraenkel (Vienna) investigation by J. C. Krantz and co-workers in 1947. Intermediate between ethyl and vinyl ether. S found it less potent than ether in frogs.

**PREPARATION**—By interaction of acetylene and ethyl alcohol.



### PROPERTIES

**Physical**—Clear, colorless, mobile liquid. Pungent odor resembles ethyl ether.  $\text{M.W. } 72.10$ ; B.P.  $33.8^\circ\text{C}$ ; S.G.  $0.73$  at  $20^\circ\text{C}$ ; S.G. vapor (air=1)  $2.49$ . Solubility:  $0.8$  vol. per 100 ml. in water. Vapor tension ( $25^\circ\text{C}$ )  $468$  mm. Hg.

**Chemical**—A mixed ether. Hybrid between ethyl and vinyl ether.

**Stability**—Unstable. Polymerizes to resins, oxides, aldehydes and peroxides. Stabilized with  $0.01\%$  alpha-phenylisopropylamine. Three percent alcohol added to prevent freezing of water vapor on mask. May hydrolyze to acetylene and alcohol in acid solution.

**Impurities**—Peroxides, aldehydes, resins.

**Storage**—In brown bottles with stabilizers of  $0.01\%$  alpha-phenylisopropylamine.

**Stability in Contact**—Stable in presence of alkali in  $\text{CO}_2$  absorbent.

**Administration**—Unpleasant odor. Induction rapid. (1) Usually by open drop; (2) by semi-closed system with air oxygen or nitrous oxide; (3) by closed system.

**Solubility**— $\text{O}_2$ /water coefficient  $48$  at  $25^\circ\text{C}$ .

**Flammability**—Lower limit  $2.1\%$  in air.

**Elimination**—Unchanged. Not hydrolyzed in the body.

**Induction**—Smooth, rapid, no breathholding. Longer if ether shorter than with ethyl ether.



### USES

- (1) To fortify nitrous oxide.
- (2) As an induction agent for ether.
- (3) For surgical procedures not requiring
- (4) As an analgesic.

### DISADVANTAGES

- (1) Unpleasant odor
- (2) Neurovascular phenomenon.
- (3) Salivation.
- (4) Nausea and vomiting.
- (5) Muscle relaxation poor.
- (6) Flammable—fire hazard.
- (7) Convulsions may occur (as with vinyl ether).
- (8) May cause headache in certain patients.

### ADVANTAGES

- (1) Induction more rapid than ethyl ether—less than vinyl ether
- (2) Emergence more rapid than ethyl ether—less than vinyl ether
- (3) Lower volatility than vinyl ether
- (4) Marginal between respiratory arrest and circulatory arrest wide
- (5) Overdose phenomenon reversed easily
- (6) May be administered by open method.
- (7) Quickly exhausted, suitable for ambulatory patients.

**Cerebrum**—Shows excess cortical activity characteristic of compounds with vinyl radical. Neurovascular phenomena less than with vinyl ether. May cause headache.

**Medulla—Respiratory Center**—Depressed. Respiration ceases before circulation.

**Forebrain Center**—Depressed in deep anesthesia.

**Vagus Center**—Increased activity absent.

**Emesis Center**—Nausea and vomiting common but less than with ethyl ether and more than with vinyl ether.

**Lungs**—Etiolates respiratory activity as does ethyl ether but not to same degree. More than with vinyl ether. No pulmonary irritation.

**Liver**—Some retention of B.S.P.

**Kidney**—No significant changes in function postoperatively.

**Sphincters**—Not relaxed.

**Muscles**—Relaxation inadequate for major surgery. Requires supplementation.

**Skin**—May cause burns if contacts.

**Intracranial Pressure**—No clinical evidence of increased pressure.

**Eyes**—May cause irritation. Signs of anesthesia similar to those of vinyl ether. Raving eyeballs become fixed in Stage IV.

**Nervous Membranes**—Slight irritation. Greater than vinyl ether—less than ethyl ether.

**Salivary Glands**—Marked salivary secretions without atropine.

**Larynx**—Spasms possible but not common unless secretions are excessive.

**Heart**—Light anesthesia causes no significant changes. Deep anesthesia causes tachycardia, ventricular and auricular extrasystoles in 1 of 4 or 5 patients.

**Blood Pressure**—Tends to fall in deep anesthesia. Unchanged in light or moderate depth.

**Gastro-intestinal**—Nausea and vomiting less frequent than with ethyl ether more frequent than with vinyl ether.

**Uterus**—Passes placental barrier. Does not relax uterus. Inhibits uterine activity in deep anesthesia.

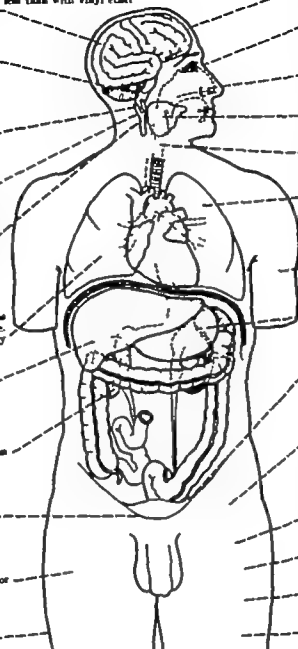
**Muscles**—Relaxation not adequate for major surgery. Not as great as with ethyl ether. Greater than with vinyl ether. Trembling movements and convulsions may occur but less frequent than with vinyl ether.

**Reflexes**—Superficial reflexes obtunded.

**Blood—Urine**—Not elevated.

**CO<sub>2</sub> Combining Power**—Not changed.

**Clotting Time**—Prolonged 10-15%. Not of clinical significance.





**Intracranial Pressure**—No clinical evidence of increased pressure.

**Respiratory Center**—Not depressed during analgesia or light anesthesia. Depression occurs as anesthesia deepens into lower planes.

**Emetic Center**—Nausea and vomiting occur in post-operative patient but no greater than with other ethers.

**Lungs**—Not irritating to alveolar membranes. Minute volume exchange increased but not to same degree as with ethyl ether. Tachypnea develops as anesthesia deepens. In spite of increased rate decreased tidal volume occurs. Tachypnea masked by narcotic premedicants. Respiratory acidosis develops as anesthesia deepens.

**Liver**—No change in bromsulphalein excretion. Biliary turbidity unchanged. No pathologic changes.

**Kidney**—No pathologic changes. No significant changes in urea clearance.

**Sphincters**—Not relaxed. Muscle relaxation poor.

**Blood**—Glucose not changed. Urea nitrogen,  $\text{CO}_2$  combining power unchanged. R.B.C., W.B.C. not changed in number or morphology. Bleeding and clotting time unchanged. Concentration in venous blood—analgesia 17 mgm. Plane I up to 60 mgm. per 100 cc.; plane 2—45 mgm. plane 3—65 mgm.; plane 4—85 mgm. spaces—80 mgm. Blood level falls from 25 to 4 mgm. in 4 minutes. More carried by blood cells than plasma.

**Cortex**—Cumulative effects not observed. E.E.G. levels similar to ether.

**Six patterns**

I—Resting alpha rhythm replaced by activity of 12-18 cycles per second—Voltage 25-80 microvolts.

II—Waves of slower frequency—4-6 cycles voltage up to 50 m.v. appear as spindles superimposed on previous fast activity—Last 2-3 sec.

III—Fast activity pattern ceases. Dominant waves increase in voltage and frequency. W ves—2-3 cycles per second at 100-300 microvolts.

IV—Irregular slow waves at 100-300 microvolts and 2-4 cycles per second. No tendency to repetition.

V—Irregular slow high voltage waves of long duration appear at 1-2 seconds with a 1-2 second spread and from 100-175 microvolts. These are superimposed on fast waves of 2-3 cycles per second with 25-75 microvolt amplitude.

VI—Slow wave frequency decreases to 1 every 18 seconds. Superimposed waves of 2-3 cycles per second at 25-50 microvolts which appear only between dominant waves.

**Eyes**—Signs similar to vinyl ether.

**Mucous Membranes**—Not irritated. Mucous formation occurs but less than with ethyl ether.

**Pharynx**—Pharyngeal reflex abolished. Air is tolerated.

**Salivary Glands**—Salivation and mucous secretions minimal. Less than ethyl ether.

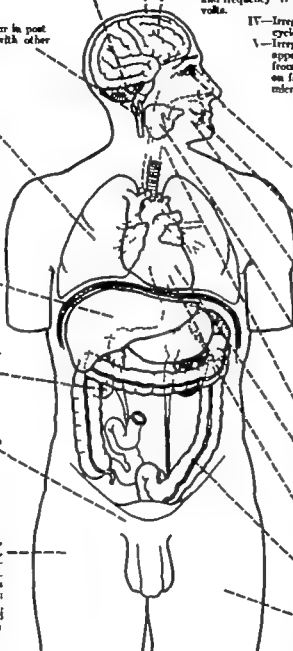
**Larynx**—Spasm uncommon.

**Heart**—Increase in pulse rate. Does not sensitize heart to epinephrine. Arrhythmias uncommon.

**Blood Pressure**—Hypotension in deep anesthesia. No depression in light anesthesia.

**Gastro-Intestinal**—Nausea and vomiting occur.

**Muscles**—Muscle relaxation not adequate for major surgery. Requires supplementation. Jaw muscles tend to remain rigid.





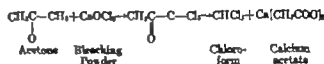
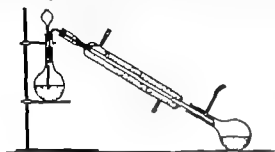
## LESS COMMON ETHERS

[illegible]

## CHLOROFORM

**HISTORY**—Prepared by Liebig, Soubeiran and Guthrie independently in 1831. Anesthetic properties discovered by Florens in 1847 on animals and by Simpson in 1848 on man at the suggestion of McWaldie and Duncan at Edinburgh.

**PREPARATION**—Most common method is to chlorinate ethyl alcohol or acetone in the presence of alkali. Chlorine and sodium hydroxide or bleaching powder may be used.



## PROPERTIES

**Physical**—A clear limpid heavy fluid possessing sweet, pleasant odor somewhat irritating. Molecular weight 119.5; specific gravity of vapor 4.12 (air equals 1); boiling point 61°C.; melting point -63°C. One cc. dissolves in 10 cc. H<sub>2</sub>O at 20°C.

**Chemical**—Decomposed by alkalis to formates. Easily oxidized to phosgene when heated. Chemical name is trichloromethane.

**Impurities**—Aldehydes, ketones, ethyl alcohol, esters, phosgene and formate. Formation of phosgene counteracted by addition of 1% alcohol which combines to form ethyl carbonate and ethyl chloride.



**Storage**—In dark, light-tight bottle with 1% alcohol, protected from light, heat and air. Included in U.S.P.

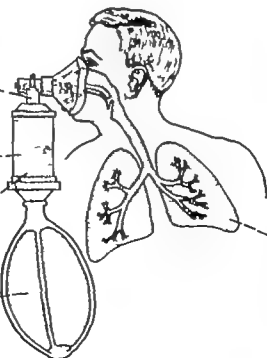
## ADMINISTRATION

By the open drop or closed technique. High O<sub>2</sub> in closed system protects against liver damage. May be insufflated or used in semi-closed system with nitrous oxide. Also used in combination with other drugs such as ether and alcohol (A.C.E. mixture).

**Effective Inspired Concentrations**—Analgesia 0.25%–0.75%; light anesthesia 0.75%–1.25%; deep anesthesia 1.25%–1.85%; respiratory arrest 2% in inhaled mixture. As much as 4% may be needed during induction.

**Stability in solution**—Not entirely stable. Small amount of formic acid forms by interaction with alkali. Formic acid reacts with the alkali to form sodium formate (formalin).

**Induction**—Rapid, not unpleasant and not accompanied by discomfort and unpleasantness noted with ether.



**Solubility**—High lipid, low water solubility. Oil-water coefficient 100 at 20°C. Concentration in body fluids varies with nature of the body fluid and tension of the vapor inhaled. Concentration greater in red cells than in plasma; air/blood distribution at 27°C. = 10.5.



**Ignitability**—Type-V per non-inflammable and does not support combustion. Oxidized in presence of flame to phosgene, which is irritating if inhaled.

**Elimination**—Not altered within the body. Major portion eliminated through lungs. Approximately 80% eliminated five to seven minutes after conclusion of anesthesia. Traces may appear in exhalations for as long as 6 hrs. Traces also appear in urine, sweat, milk and excreta of gastrointestinal tract. Possibility of small amount being altered and causing liver damage not excluded but not proved.

**Brain**—Pathways carrying sensory impulses from periphery to cortex interrupted. Cerebral metabolism depressed. Concentration of drug increased in brain before other tissues.

**Temperature Regulating Center**—Depressed. Body temperature tends towards environmental temperature.

**Respiratory Center**—Depressed in deeper planes of anesthesia threshold to  $\text{CO}_2$  raised.

**Thermometer Center**—Not affected in light anesthesia. Depressed in deeper planes of anesthesia.

**Touching Center**—Depressed. Nausea and vomiting in post-anesthetic period common. Most probably due to central effect.

**Taste Center**—Depressed in deeper planes of anesthesia; active in light anesthesia. Vago-vagal reflexes possible.

**Cerebral Body**—Remains active.

**Cerebral Spinal**—Depressed in deeper planes of anesthesia.

**Thyroid**—No notable effect. Repeated administration of thyroid decreases resistance to drug.

**Eye**—Respiration increased in rat and depth during induction and in light anesthesia. Minute volume exchange decreased in deeper planes of anesthesia. Accommodation reflex, pupillary reflex, bronchial muscle relaxed. Secretions increased. No change in vitreous membrane.

**Iridium**—Depressed.

**Esophagus**—No notable change in upper portion of anesthesia. Movements decreased in deep anesthesia.

**Mouth**—Depletion of esophageal content. Release of esophageal during excitement and induction period thought to reduce retrograde circulation in face of increased cardiac mobility.

**Stomach**—Function temporarily impaired as measured by tympanophagus retention, pectate and fraction tolerance tests. Glycogen, three-fourths depleted in first half hour; low rapidly restored. Bile formation decreased. (via formation normal. Prothrombin time prolonged. Bile pigments increased in blood. Severity and duration of dysfunction varies with depth of anesthesia. Hepatitis may follow.

**Liver**—Oliguria during anesthesia, followed by polyuria during recovery possibly due to release of anti-diuretic hormone. Albumin appears in one-third of cases. May aggravate existing renal damage.

**Pulmonary**—Dilated.

**Intracranial Pressure**—Increased slightly. Spinal fluid of significance without anoxia or hyperoxia.

**Eye**—Eyeball movements remains active in plane (pts) considered in planes 1 to 3. Dilated during Corneal reflex remains active into plane 3. Lg.

**Mucous Membranes**—Irritated. (Irritated. Mucus secretion increases.

**Salivary Glands**—Stimulated at periphery during anesthesia. Mucus secretion increased.

**Pharynx**—Mucous not irritated reflex depressed. Pharyngeal a III Thick mucus secreted if larynx respiration due to apnea occurs if anoxia is present.

**Larynx**—Laryngeal concentrations. (Irritated in plane Vagovagal reflex inhibition of respiration.

**Heart**—Myocardium plane of anesthesia. (Irritated in plane Vagovagal reflex inhibition of respiration. Also cause cardiac sudden death. All tissues in respiratory arrest. Ventricular fibrillation follows. Proximal reflexes reduced output decreased.

**Blood Pressure**—Little changes. (Irritated in plane Vagovagal reflex inhibition of respiration. Also cause cardiac sudden death. All tissues in respiratory arrest. Ventricular fibrillation follows. Proximal reflexes reduced output decreased.

**Visceral Pressure**—Rig planes. (Irritated in plane Vagovagal reflex inhibition of respiration. Also cause cardiac sudden death. All tissues in respiratory arrest. Ventricular fibrillation follows. Proximal reflexes reduced output decreased.

**Spleen**—Contracted. (Irritated in plane Vagovagal reflex inhibition of respiration. Also cause cardiac sudden death. All tissues in respiratory arrest. Ventricular fibrillation follows. Proximal reflexes reduced output decreased.

**Stomach**—Movements of tone decreased. (Irritated in plane Vagovagal reflex inhibition of respiration. Also cause cardiac sudden death. All tissues in respiratory arrest. Ventricular fibrillation follows. Proximal reflexes reduced output decreased.

**Intestines**—Movements inhibited. (Irritated in plane Vagovagal reflex inhibition of respiration. Also cause cardiac sudden death. All tissues in respiratory arrest. Ventricular fibrillation follows. Proximal reflexes reduced output decreased.

**Pancreas**—Blood sugar.

**Uterus**—Contractions at anesthesia abolished in deep anesthesia. (Irritated in plane Vagovagal reflex inhibition of respiration. Also cause cardiac sudden death. All tissues in respiratory arrest. Ventricular fibrillation follows. Proximal reflexes reduced output decreased.

**Blow**—Vessels dilated. Temperature elevated. Irritated.

**Skeletal Muscles**—Slight reduction in tone in plane (pts) considered in planes 1 to 3. Complete relaxation in pts.

**Body Temperature**—Decreased 1 to 4°F due to deepening center peripheral vascular dilatation and

**Total Blood Volume**—Decreased. Varies with duration and depth of anesthesia.

**Red Blood Cells**—Increased in number. Immediate decrease in fragility due to damage to stroma. Sedimentation rate decreased. No hemolysis occurs *in vitro*. Hemoglobin increased.

**Leukocytes**—Increased in post-anesthetic period. If return to normal within 48 hours. If abnormal within 48 hours. Polymorphonuclear cells increased relatively and absolutely. Morphology unchanged. Decrease in phagocytosis.

**Platelets**—Unchanged.

**Clotting Time**—Decreased after one-half hour. Prothrombin time prolonged.

**Oxygen Capacity and Content**—Capacity increased. Blood specific gravity increased. Viscosity increased. Oxygen content reduced in deep anesthesia.

**Total Carbon Dioxide**—Increased.

**Carbon Dioxide Combining Power**—Decreased shortly after onset of anesthesia. pH decreased. Gradual return to normal after recovery.

**Concentrations**—43% in red cells (more than blood content allows—possible combination with proteins).

**Concentrations**—80 to 90 mgm. per 100 cc. of blood. 90 to 40 depressed 40 to 60 fatal.

**Glucose**—Increased up to 800%.

**Lipids**—Slight increase in total lipids. Considerable sustained increase if hepatitis occurs. Unsaturated fatty acids and cholesterol fractions increased over neutral fats.

**Lipase**—Increased if hepatitis occurs.

**Amino Acids**—Increased if post-operative hepatitis occurs.

**Non-protein Nitrogen**—Normal in 24 hours. Increases with return to normal during recovery. Elevated if hepatitis occurs.

**Urea**—Increased during anesthesia. Decreased if post-operative hepatitis occurs.

**Ammonia**—Increased if post-operative hepatitis occurs.

**Phosphates**—Decreased during, but increased in recovery period.

**Bile**—Increased if hepatitis occurs. Slight increase otherwise.

**Ketones**—Appear during terminal phase of prolonged anesthesia.

**Bromine**—Decreased during anesthesia.

**Iodine**—Decreased during anesthesia.

# URINE

**Urea**—Decreased during anesthesia. Ammonia may occur.

**Chlorides**—Increase after anesthesia.

**Phosphates**—Decrease during and increase for few hours after anesthesia.

**Glucose**—Not present.

**Reflex Action**—Drug which paralyzes act. urine may give false positive tests for sugar.

**Nitrogen**—Total nitrogen decreased during and increased after anesthesia.

**Albumin**—Present in one-third of cases.

**Hepatitis with Liver Damage**—Bile increases. Ammonia increases; amino acids increase; urea decreases.

**Blood**—May occur if hepatitis occurs.



# THE PHARMACOLOGY OF ANESTHETIC DRUGS

## PATHOLOGY



**Causes**—Prolonged administration over 90 to 100 minutes or administration while blood pressure is reduced may be followed by hepatitis. Starvation may predispose. Feeding glycerol, antibiotics, amino acids and protein. Food protective action. Anoxia enhances effects. Admixture with oxygen decreases incidence. May be result of decomposition of part of chloroform to haloacetaldehyde in liver.

**Symptoms**—Those of acute toxic hepatitis. Fever, jaundice, bleeding tendency, reduced liver function, bile and plasma chloroform amino acids in urine, reduced serum prothrombin time, prolonged bleeding and clotting time, increased serum bilirubin.

**Changes in Liver**—Cloudy swelling followed by necrosis of cells in center of liver lobules surrounding central vein. Changes appear 6 to 10 hours after cessation of anesthesia. Become maximal in 48 to 72 hours. Liver becomes atrophic. Death may occur on 4th or 5th day. Regeneration follows survival. Fibrous scar tissue crept in cases of chronic poisoning following repeated administration.

**Changes in Other Organs**—Fatty degeneration in tubules of kidney. Glomeruli not altered. Cloudy swelling of myocardium. Hemorrhagic subserosa areas throughout tract due to hemorrhagic subserosa of placenta. Hemorrhagic areas in parenchyma of placenta. Necrotic areas in placenta of pregnant females.

## USES

- (1) As an analgesic in obstetrics and minor surgical procedures.
- (2) As a preliminary or induction agent for ether.
- (3) For major surgery requiring relaxation.
- (4) For use when caution or electro-surgical unit are required.
- (5) For securing extreme degree of relaxation of uterus in obstetrics (Band's ring).

## ADVANTAGES

- (1) Yields excellent relaxation.
- (2) Induction is rapid, not unpleasant and does not require use of a preliminary induction agent such as nitrous oxide or ethylene.
- (3) It is non-irritant.
- (4) Very simple equipment may be used to administer it—mask and dropper bottle.
- (5) Volatility is of such a degree that it may be used in tropical climates.
- (6) Respiration is not markedly stimulated or depressed.
- (7) Low concentration required for surgical anesthesia allows air to be used as vehicle and source of oxygen.
- (8) Chemically stable and easily preserved.
- (9) Inexpensive.

## CONTRAINDICATIONS

- (1) Cardiac diseases.
- (2) Hypertension.
- (3) Hypotension (shock).
- (4) Diabetes mellitus, or acidosis from any cause.
- (5) Hepatitis or liver dysfunction.
- (6) Renal diseases.
- (7) Acute respiratory infections.
- (8) Is emaciated, cachectic "wreck" or acutely ill patient.
- (9) In hands of the inexperienced.

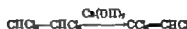
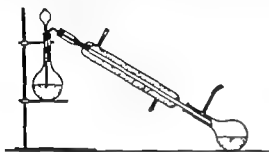
## DISADVANTAGES

- (1) Possesses a narrow margin of safety.
- (2) Depresses myocardium. Concentration causing respiratory arrest also causes serious cardiac failure.
- (3) Scatters the automatic tissues of the heart, causing arrhythmias.
- (4) Causes arrhythmias, even ventricular fibrillation with v arrhythmias.
- (5) Causes anaphylactic shock.
- (6) Hepatitis may follow in the post-operative period.
- (7) Severe biochemical and metabolic disturbances follow.
- (8) Severe, cautionary sparks, or oxidize it to phosgene, a gas of lethal, causing pulmonary edema.
- (9) Elimination is slow.
- (10) Of questionable safety.
- (11) Post-anesthetic nausea and vomiting very common.
- (12) Irritating to skin and mucous membranes.
- (13) Not easily volatilized at ordinary room temperature.

## TRICHLORETHYLENE

**HISTORY**—First described in 1864. Plesner discovered analgesic properties in 1917. Studied as an anesthetic by Dennis Jackson and co-workers (Cincinnati) in 1935 in U. S. and used in limited number of clinical cases. C. L. Hewer, England revived interest in it in 1939 in search of a potent, non inflammable anesthetic.

**PREPARATION**—Acetylene is chlorinated to form tetrachlor ethane which is boiled with lime.

**PROPERTIES**

**Physical**—Clear colorless fluid, possessing an odor somewhat similar but less pungent than chloroform. B.P. 67°C. M.W. 130—S.G. 1.47 at 15°C. Vapor heavier than air (S.G. 4.83)

**Chemical**—Stable under ordinary circumstances. Decomposed by light and heat and air. Mixes with ether in any proportion. Compatible with nitrous oxide.

**IMPURITIES**

Decomposed by oxidation to dichloroacetyl chloride, hydrochloric acid and phosgene. Decomposition retarded by 0.01% thymol. Often colored with methylene blue to distinguish it from chloroform. Impurities detected by testing with Congo Red for the hydrochloric acid, silver nitrate for aldehydes and radium iodide and starch for free chlorine.

**STORAGE**

Packed in amber bottles to protect from light.

**ADMINISTRATION**

By inhalation using the open, semi-open insufflation or semi-closed techniques. Cannot be used with soda lime or Baralyme as the closed technique. Vaporizers slowly to open technique. Best results are with semi-closed method using nitrous oxide and oxygen.

**Induction**—Pleasant and comparatively rapid. Longer than cyclopropane. Non-irritating. V. poured with difficulty.

**Concentrations**—Analgesic—0.1-2% anesthetic—0-7.5%.

**SYNONYMS**

Trilene, chlorylene, westronol.

**STABILITY**

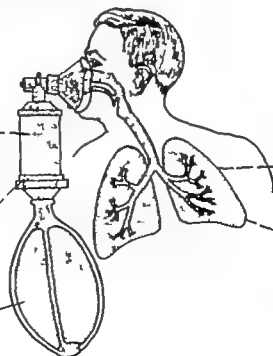
Not stable in the presence of alkaline absorbents. Forms dichloroacetylene, which is explosive and phosgene. Both are toxic if inhaled. Heat accelerates decomposition of agent.

**SOLUBILITY**

Highly soluble in lipoids. Insoluble in water.

**INFLAMMABILITY**

Not inflammable in concentrations below 10% with air or oxygen. Vapor mixed with pure oxygen may ignite above 66°F but not if mixed with air.



**Elimination**—Unchanged through the lungs and other channels of excretion. Partial decomposition of small percentage of drug in body believed to occur.

**Recovery**—Rapid after brief administration of light anesthetics.

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

50

**Cortex**—Depressed. Has potent anesthetic effect. Onset rapid. Causes anaesthesia. Depresses cortical potentials (see electroencephalogram.)  
**Faciculus Center**—Apparently not affected in moderate depths of anaesthesia. Depressed in deep anaesthesia.  
**Respiratory Center**—Depressed in Stage III.

**Cough Center**—Depressed.

**Swallowing Center**—uses acid crystals in post-anaesthetic period in 80% of cases. Uncommon when used for anaesthesia or with nitrous oxide.

**Cerebral Nerves**—1. absorbable to hypodermic injections. Soda lime slowly converts drug to dichloroacetylene which causes bilateral anaesthesia of VIIth nerve. If inhaled Complication more apt to occur in patient who follows one inhaling drug into lower system after periods of anaesthesia. Patient receiving drug not necessarily affected. Pure drug not specific for VIIth nerve.

**Lungs**—Tachypnea frequent during anaesthesia—rate may be as high as 60 + 100. Mucous membrane exchanges may be reduced in spite of rapid rate due to stimulation of deflation receptors in alveoli. Tachypnea stops after deep anaesthesia. Reflex obtained by isopropyl and other narcotics.

**Liver**—Impairs excretion of bromocephalene. Physiological changes follow prolonged or repeated use of drug. Detoxified up to 15% by conversion to chloral reduction to trichloroethanol and oxidation to trichloroacetic acid.

**Kidney**—Renal clearance unchanged. Urea values unchanged. Oxidized biproduct (trichloroacetic acid) eliminated into urine. Function not decreased during anaesthesia.

**Body Temperature**—Usually falls. Temperature regulating center depressed. Unchanged when used for anaesthesia.

**Blood**—No change in sugar or non-protein nitrogen. No change in blood cell morphology.

## USES

- (1) As an anesthetic with air (in Cyanide or Dike Inhaler)
- (2) For light anaesthesia not deeper than first plane in combination with nitrous oxide by the semi-closed technique.

## ADVANTAGES

- (1) Is potent anesthetic for anaesthesia and minor surgery
- (2) Is not flammable.
- (3) Not unpleasant to inhale.
- (4) Inexpensive.
- (5) May be used for ambulatory patients

**Intracranial Pressure**—Not changed. Suitable for neurosurgery and  $N_2O$  changes with analgesia.

**Eye**—Movements of eyeballs persist late lower planes. Pupils readily dilate in deep anaesthesia.

**Mucous Membranes**—Not irritated by anesthetic.

**Salivary Gland**—Stimulated during inhalation. Secretion decreased during maintenance.

**Larynx**—Not irritated in anesthetic concentrations. Cords relaxed. Spasm not common. Laryngeal reflex abolished in lower planes.

**Heart**—Cardiovascular. Less so if used with  $N_2O$ . Irregularities common. Arrhythmia caused by increased vagal tone. Later during first and second plane ectopic (not in aortic and ventricle) give way to regular tachycardia. Enhanced by epinephrine. No effect on coronary vessels.

**Blood Pressure**—No significant deviation during surgical anaesthesia. Falls in deep anaesthesia. Causes hypotension.

**Colon**—Absorbed from colonic mucosa via administered rectally.

**Uterus**—Suitable as anesthetic for short. Not inhibited during anaesthesia. Passes into fetal circulation. No hyperventilation if used for anaesthesia.

**Muscles**—Relaxation not always mild. Activity marked during early plane of anaesthesia.

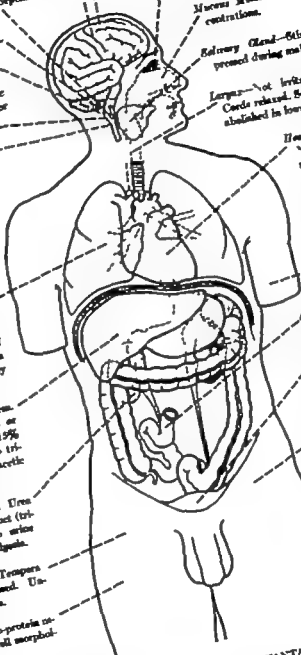
**Reflexes**—Not completely abolished. Frequently move when stimuli in deeper planes of anaesthesia.

**Skin**—Dermatitis follows from repeated use on second skin on contact with pressure.

**Tolerance and Habituation**—Not reported.

## DISADVANTAGES

- (1) Not satisfactory as surgical anesthetic for major surgery
- (2) Cannot be used in the closed system.
- (3) Muscle relaxation poor
- (4) Is cardiotoxic and causes disturbances in cardiac rhythm.
- (5) May be hepatotoxic
- (6) Vaporizes with difficulty



## FLUOTHANE (HALOTHANE)

## SYNONYMS—Halothane

**HISTORY**—Synthesized by Sockling (1951) Basic animal studies reported by J. Raventos (1956) Studies in man by Michael Johnstone (1956) and Bryce Smith and O'Brien (1956) (all in England)

**PROPERTIES**

**Physical**—Clear, mobile liquid, B.G. 1.88 (40°C.) B.P. 50°C. at 760 mm. Hg Vapor pressure 841.5 mm. Hg at 40°C. Solubility 0.844 parts in 100 part H<sub>2</sub>O at 40°C. Oil/water ratio 250.

**Chemical**—Stable Decomposes to various acid products if exposed to light. Stabilized by addition of thymol (0.01%) Presence of fluorine on carbon 1 stabilizes of chlorine and bromine on carbon 2.

**In practice**—Decomposed by acids but halogenated acids.

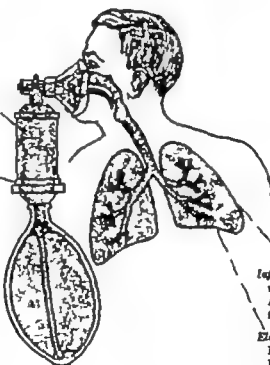
**Storage**—In dark bottles.

**ADMINISTRATION**

By semi-closed, non-rebreathing techniques using precision calibrated heat compensated vaporizers. Inhaled concentration difficult to control in both closed system and open techniques. Not decomposed by soda or Baralyme.

**Induction**—Smooth without struggling Stage II quiet and uneventful. Induction and recovery rapid. Less than 4 minutes in short procedures. 0.5-0.8% required for induction. Maintenance accomplished with 0.4-1.0%.

**Maintenance**—Little additional agent necessary after induction. Not easily controlled unless temperature compensated vaporizer is used. Conventional draw-over type of vaporizer not satisfactory particularly in closed system.



**Inflammability**—Vapors not flammable when mixed with air nitrous oxide or oxygen. Azeotropic mixtures with ether (94%) fluorothane (80%), not flammable.

**Elimination**—Not altered within the body. Major portion eliminated through lungs. Recovery occurs within 5-8 minutes. Minimize traces persist on exhalation due to elimination of drug absorbed by adipose tissues. Longer recovery period in long anesthetics (up to 100 minutes).

**USES**

When non-flammable anesthetic is desired

**ADVANTAGES**

- (1) Non-flammable.
- (2) Non-irritating.
- (3) Non-spasmodic to larynx and bronchi.
- (4) Rapid induction and recovery.
- (5) Potent—more potent than chloroform.
- (6) Chemically stable.
- (7) Fortifies nitrous oxide.

**DISADVANTAGES**

- (1) Overconcentration leads to circulatory collapse.
- (2) Expensive.
- (3) Difficult to use in closed systems or by open-drop method.
- (4) Depresses respiration and circulation.
- (5) Enhances ganglionic blockade.



## FLUOTHANE

**Brain**—Depresses from above downward. Somewhat clear after recovery. Follows stage and planes according to Guedel. Electroencephalogram similar to ether—7 levels:

Level I—Fast frequency low voltage activity as consciousness is lost.

Level II—Slow frequency 8-8 cycles per second; high voltage of 50 microvolts in light surgical. Fast low voltage activity superimposed.

Level III—Slow waves 4 cycles per second. Amplitude of 80-100 microvolts.

Level IV—Fast activity disappears 8-8 cycles per second, 80-100 microvolts.

Level V—Slow waves 1 cycle per second 100-200 microvolts interspersed with smaller fast waves 15-20 minutes, 8-8 cycles per second.

Level VI—Slow wave frequency 8-8 cycles per second, amplitude 15 microvolts. First burst suppression.

Level VII—Absence of any wave forms.

**Forcing Center**—Depressed during anesthesia. Nausea and vomiting uncommon in post-anesthetic period.

**Cough Center**—Obtunded.

**Respiratory Center**—Depressed by deep anesthesia. Respiratory arrest precedes cardiac arrest. Response to 5% CO<sub>2</sub> diminishes with increasing depth.

**Respirator Center**—Some depression giving rise to hypoxia.

**Vagus Center**—Vagal action preserved or enhanced. Bradycardia develops. Atropine premedication desirable.

**Cardiac Body**—Remains active.

**Lungs**—Respirations deep and regular in upper stages. Depressed in lower stages. Tidal volume decreases as anesthesia deepens. Rate increased to compensate for decreased tidal volume, minute volume unchanged. End expired CO<sub>2</sub> tension rises as anesthesia deepens. Preoxygenation reduces respiratory depression.

**Trachea**—Not spasmogenic. No irritation, cough or secretion.

**Metabolism**—Decreased. Body temperature falls due to decreased activity.

**Liver**—Moderate increase in bromsulphalein retention (same as ether less than chloroform). Thyroid activity unchanged after 8 days. No change in succinate or benzoic acid. Serum transaminase unchanged after 14-20 hours.

**Adrenal**—Sympathetic activity not depressed.

**Kidney**—Urea clearance not affected. Blood urea remains normal. No microscopic changes in urine.

**Blood**—Volume unchanged. Bleeding and clotting time unchanged. Decreased coag. time to hypoxia.

**Cells**—No changes in morphology.

**Spleen**—Moderate atrophy.

**Uterus**—No change.

**Gases**—Total CO<sub>2</sub> content and CO<sub>2</sub> tension fall as anesthesia deepens and ventilation is decreased.

**Concentration**—Blood P.E.G. level I—0.8 mg. per 100 cc. Level II—0.5 Level III—7.1; Level IV—0.5 Level V—80.

**Pathology**—No specific lesions attributable to drug.

**Intracranial Pressure**—Not elevated to any significant degree. Satisfactory for neurological surgery.

**Temperature Regulating Center**—Depressed in surgical stages of anesthesia.

**Eye**—Lid reflex disappears Stage IV plane 1. Pupils contract in Stage III. Do not dilate as anesthetic deepens. Rotation of eyeballs ceases at plane 2. Corneal reflex remains active plane 1 and 2. Pupils dilate in deep anesthesia.

**Mucous Membranes**—Not irritated by inhaled anesthetic concentration.

**Salivary Glands**—Not atrophied. Absence of secretion.

**Pharynx**—Reflex disappears in plane 1. Pharyngeal airway tolerated.

**Larynx**—Not spasmogenic. Spasm uncommon after failure at intubation. Tube tolerated. Non-irritating to mucous membrane in anesthetic concentrations.

**Heart**—Depresses myocardium. Causes decrease in cardiac output. Stages decrease in cardiac output. Stages decrease in pulse bradycardia—10% decrease in pulse bradycardia with concentration. Arrhythmias appear in deep anesthesia with all techniques. Escape may occur. Ventricular ectophasia may develop. Ventricular tachycardia may develop. Atrial rhythm and escape may occur. Heart sensitized to pressure changes, particularly sympathetic and vagal stimulation.

**Brain Pressure**—Hypotension consistently observed. Proportional to concentration. Greater during induction than during maintenance. Probably result of decreased cardiac output and depression of ventricular center. Ganglionic blockade may also play minor role. Not reversed by atropine.

**Hypotension**—Disappears during maintenance, unless overconcentration produces myocardial depression.

**Adrenergic Nervous System**—Not a potent ganglionic blocking agent by itself, but tentative ganglionic blockade by a methohexal and d-tubocurarine.

**Venous Pressure**—Tends to increase.

**Atrial Pressure**—Some increase in peripheral arteries indicating some sympathetic activity.

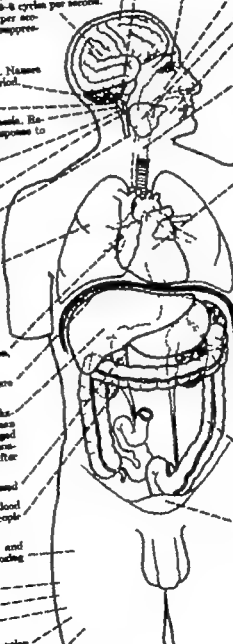
**Gastro-intestinal**—Nausea and vomiting common. Depresses visceral smooth muscle.

**Uterus**—Inhibited progressively as depth deepens. Escapes to a large drug plasma placental barrier.

**Muscles**—Concentration up to 4.0% paralysis neuromuscular junction. Atrial myoelectric activity effect slightly as testicular d-tubocurarine. Satisfactory spasm for major surgery.

**Body Temperature**—Decreased due to loss of heat regulating center.

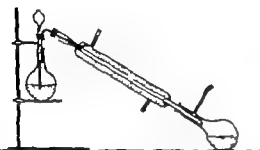
**Mucous**—Temperature elevated. Viscid. Dry, warm, pink. No blistering with pooled locally.



## ETHYL CHLORIDE

**HISTORY**—Prepared by Basil Valentine in 17th century. Anesthetic properties discovered by Pierre Flourens of France in 1847. P. Redard of Switzerland in 1888 introduced it as a spray for local anesthesia. H. J. Carlson, Swedish dentist, accidentally caused general anesthesia in man while using a spray for local anesthesia. Used for general anesthesia by Redard in 1888 in Switzerland.

**REPARATION**—(1) By reacting ethylene with gaseous hydrogen chloride. (2) By refluxing ethyl alcohol with hydrochloric acid and zinc chloride.



## PROPERTIES

**Physical**—Gas at ordinary temperature which readily compresses to a clear, liquid, colorless, non-irritating, boiling point  $-12.5^\circ\text{C}$ ; molecular weight 64.5; specific gravity 0.907 at  $20^\circ\text{C}$ ; specific gravity of vapor 2.98 (air equals 1); vaporization reduces temperature to below freezing. Temperature attained is between  $-15$  to  $-20^\circ\text{C}$ . Soluble in alcohol and ether. 1 cc. of liquid in 8 liters air = 7% mixture of vapor.

**Chemical**—Hydrolyzed by acids and alkalis in alcohol. Decomposed by light and heat in the presence of water. Burns with green flame.

**Stability**—Stable at room temperature. Decomposed by light and air.

**Impurities**—Alcohol, ether, hydrochloric acid, and ethyl alcohol.

**Storage**—Store in rubber container as liquid under slight pressure. Equipped with a fine capillary nozzle and tight cap. Holding a fine spray two or three feet long to ensure being in cool place. Labeled in U.S.P. XIII. Also known as *Keloid*, *mercurial chloral*, *mercurial chloroethane*.

**Stability in Air**—(1) Hydrolyzed slowly by the alkali metal chlorides and ethyl alcohol.

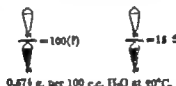
## ADMINISTRATION

**Open-drop**, or closed technique. Ice from condensed water vapor forms on mask. Ice used by open-drop method.

**Induction**—Rapid, 1 to 2 minutes. Pleasant and easy to inhale. No excitement.

**Effective Concentrations of Inhaled Mixtures**—Anesthesia—1 to 8%; narcosis—3 to 5%; to 4.5% respiratory failure 6%.

**Solubility**—Possesses high lipid solubility; at  $35^\circ\text{C}$ , 8 volumes of vapor dissolve in 1 volume of blood. Slightly soluble in water.



**Inflammability**—Ignition temperature  $517^\circ\text{F}$ . 1 pound with air makes 117 cubic feet of explosive vapor.  $180^\circ\text{F}$  at normal pressure. Minimum ignition temperature in air  $825^\circ\text{F}$ ; in oxygen  $874^\circ\text{F}$ .

With Air



With Oxygen

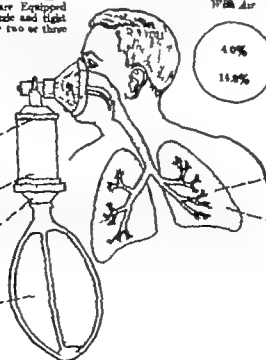


In Nitrous Oxide



**Elimination**—Major portion eliminated unchanged in urine, feces, sweat and exhalation. Recovery from anesthesia rapid requiring 1 to 2 minutes. Minor traces remain in blood for some time after discontinuing anesthesia. Greatest portion exhaled. Possibility of decomposition of some portion in body not disproved.

**Difference**—Absorbed from isolated lung lobule in 18 minutes (air = 16 hrs.)



# THE PHARMACOLOGY OF ANESTHETIC DRUGS

**Cortex**—Pathways from periphery blocked. Reflexes and motor activity abolished in stage III

**Respiratory Center**—Depressed. Respiration falls before deceleration.

**Vasomotor Center**—Depressed in deep anesthesia or in overdosage. Ordinarily not affected.

**Cough Center**—Depressed during third stage anesthesia.

**Vagus Center**—Stimulated at first, depressed in deep anesthesia.

**Vomiting Center**—Depressed. Post-anesthetic vomiting infrequent.

**Lungs**—Alveolar membrane locally stimulated. Hyperpnea occurs in first plane followed by respiratory depression. Pulmonary and bronchial epithelium not irritated to any marked extent.

**Liver**—May reduce liver function. May cause hepatitis.

**Splanchnics**—Relaxed only in deep anesthesia.

**Skeletal Muscles**—Relaxation of large muscles obtained with difficulty. Spasticity may occur. Opisthotonus and rigidity not infrequent during induction.

**Skin**—Pallor in deep anesthesia due to vasomotor collapse. Ashen gray cyanosis not uncommon in collapse.

**Blood**—Concentration, 80 mgm. per 100 cc for light anesthesia; 30 mgm. for deep anesthesia; 40 mgm. lethal. Margins of safety narrow.

**Intraocular Pressure**—Increased slightly. Not of significance without anoxia.

**Eyes**—Eyeballs continue to rotate in 1st plane. Pupils dilated in stage III; constricted in stage III. Eye signs not a reliable guide to depth.

**Mucous Membranes**—Slightly irritated. Salivary activity depressed. Secretions absent.

**Pharynx**—Pharyngeal reflex depressed in first plane. Airway tolerated. Spasms of pharyngeal muscles common.

**Salivary Glands**—Slight increase in secretion during induction, abolished during anesthesia.

**Larynx**—Cough reflex abolished in deep anesthesia. Reflex spasm of glottis frequent if induction or arousal is prevented in upper respiratory tract. Laryngeal reflex abolished in 2nd plane.

**Heart**—Primary decrease in rate (rapid of feet) followed by increase. Cardiac output decreased on average of 18%. Myocardium depressed directly. Ventricular fibrillation may occur early due to increased irritability of automatic tissues. Arrhythmias caused by epinephrine. Ventricular fibrillation may occur during induction. Overdosage results in asystole from myocardial depression.

**Blood Pressure**—Decreased in deep anesthesia due to peripheral dilatation from depressed vasomotor center.

**Gastro-intestinal Muscles**—Decreased activity of these organs.

General pharmacological effects of ethyl chloride are similar but less intense than those of chloroform. Circulatory failure may occur before respiratory failure.

## USES

- (1) For analgesia for minor operations (odontia, obstetrics)
- (2) For anesthesia for short surgical procedures.
- (3) As a preliminary in open ether anesthesia to shorten second stage
- (4) As a complement to nitrous oxide or ethylene anesthesia.
- (5) As a spray to cause local anesthesia by the production of cold.

## ADVANTAGES

- (1) Period of induction and recovery rapid.
- (2) Shortens length of stage II of ether anesthesia during induction.
- (3) Requires simple or minimum of apparatus.
- (4) Allows use of air as diluent and source of oxygen.
- (5) Does not cause respiratory depression.
- (6) Chemically stable and inexpensive
- (7) Severe or prolonged post-anesthetic vomiting absent.

## CONTRAINDICATIONS

- (1) Presence of cavity or other sources of ignition.
- (2) Presence of cardiac renal or hepatic disease
- (3) Presence of upper respiratory infections.
- (4) Procedures expected to last more than several minutes.

## DISADVANTAGES

- (1) Possesses a narrow margin of safety
- (2) Causes circulatory depression, particularly affecting the heart.
- (3) Forms explosive mixtures with air or oxygen.
- (4) Frequently causes muscle rigidity and stridor
- (5) Depth of anesthesia not easily maintained at a constant level.
- (6) May cause renal or hepatic damage

## MIXTURES OF HALOGENATED HYDROCARBONS

ANESTHOL—Ethyl chloride 1% chloroform 36%, diethyl ether 47%.

SCHLEICH'S MIXTURE—Same three drugs in different proportions.

SOMNOFORM—Ethyl chloride 35%, methyl chloride 60%, methyl bromide 5%.

NOVANESE—Ethyl chloride methyl chloride chloromethylene diethyl ether

ANESTILE—Ethyl chloride and methyl chloride

A.C.E. MIXTURE (Alkaform)—Alcohol 16% chloroform 34% ether 50%.

## LESSER KNOWN HALOGENATED HYDROCARBONS

Drug	Chemistry	Properties	Uses	Comments
Methyl chloride (monochloromethane)	Clear, colorless, odorless gas. B.P. $-24^{\circ}\text{C}$ . Compresses to a colorless liquid. Burns with a green flame.	Slightly narcotic and anesthetic when inhaled. Rapid acting, and rapid recovery.	As a refrigerant.	Toxic for clinical use. Decomposes to methyl alcohol in body. Toxic to lungs and nerve tissue. Toxic manifestations appear hours or days after inhalation.
Methyl dichloride (dichloromethane)	Clear, colorless liquid. B.P. $40-41^{\circ}\text{C}$ .	More narcotic than methyl chloride. Not inflammable—100 water at $55^{\circ}$ .	As a spray for local anesthesia. As a refrigerant.	Toxic to liver, lungs and nerve tissue. Causes abortion (features as methyl chloride). Contraindication very potent and cause permanent damage. Does not form methyl alcohol.
Carbon tetrachloride (tetrachloromethane)	First prepared by Rengault in 1830. Clear, colorless, non-inflammable liquid. B.P. $76^{\circ}\text{C}$ .	Potent narcotic if inhaled.	Antheims tic agent—Fire extinguisher.	Formerly narrow margin of safety. Hepatotoxic. Absorbed slowly. Does not form methanol in body. Not suitable for surgical anesthesia.
Methyl bromide (monobromomethane)	Clear, colorless, odorless gas. B.P. $4.5^{\circ}\text{C}$ .	Mildly narcotic, irritant.	As refrigerant and insecticide.	Short or prolonged periods of inhalation cause pulmonary irritation and various neurological changes. Toxic manifestations delayed for hours or days. Decomposes to methanol in body.
Bromoform (tribromomethane)	Prepared by Löwig in 1832. Colorless, heavy liquid. B.P. $239^{\circ}\text{C}$ .	Potent narcotic. Like chloroform in action but with narrower safety margin.	Not used clinically. Formerly used as an antispasmodic for cough.	Hepatotoxic. Not stable—decomposes to free bromine and other brominated compounds. Vaporizes slowly with difficulty. Not inflammable.
Ethyl bromide (monobromomethane)	Colorless liquid with ethereal odor. B.P. $38^{\circ}\text{C}$ . Insoluble. Not stable in presence of heat, light and air.	Narcotic, similar to ethyl chloride. More potent. More toxic.	As surface anesthetic. Inhalation anesthetic similar to ethyl chloride.	Formerly narrow margin of safety. Rapid induction and recovery. May cause pulmonary irritation.
Ethylene dichloride (dichloroethane)	Colorless, oily liquid with pleasant odor and sweet taste. Boils $83-85^{\circ}\text{C}$ .	Formerly narcotic properties.	Not used clinically.	Potency approaches that of chloroform. More potent than ethyl chloride.
Ethylene dibromide (dibromomethane)	Colorless, heavy liquid. B.P. $131^{\circ}\text{C}$ . Chloroform-like odor. Unstable in presence of light, heat and air.	Narcotic.	As solvent. Not clinically important.	Causes degenerative changes in viscera. Irritates skin and mucous membranes.
Vinyl chloride (monochloroethylene)	Colorless gas with ethereal odor. B.P. $15-16^{\circ}\text{C}$ . Inflammable.	Narcotic and anesthetic similar to ethyl chloride.	As a solvent.	Possibility as surgical anesthetic not completely investigated. May be hepatotoxic. Causes pulmonary irritation in animals.
Dichloroethylene	Colorless liquid with slightly ethereal odor. B.P. $85^{\circ}$ .	Narcotic and anesthetic.	Not clinically important.	Irritating, causes nausea, cramps, leading to sleep.
Tetrachloroethylene	Clear, colorless liquid. B.P. $121^{\circ}$ . Non-inflammable.	Formerly narcotic properties.	Tried clinically by Aspin. Found unsuitable.	Flow induction causes protein reactions. Difficult to vaporize. Not stable. Irritates skin. Used to maintain even plane of anesthesia.
Aerthol	Clear, colorless liquid.	Produces general anesthesia.	For inhalation anesthesia.	Ethyl chloride 17 parts, chloroform 53, ethyl ether 47.
Sauerform	Clear, colorless liquid.	Produces general anesthesia.	For inhalation anesthesia.	Methyl chloride 60 parts, ethyl bromide 8, ethyl chloride 32.
Alcoron (A.C.E. mixture)	Clear, colorless liquid.	Produces general anesthesia.	For inhalation anesthesia.	Chloroform 31, alcohol 11, ether 58.

## SECTION VII. INORGANIC NONVOLATILE AGENTS

### BROMIDE ION

**Cerebrum**—Depresses. Induces sleep which is never deep. Mental processes dulled. Motor cortex depressed. "Psychotic" symptoms in chronic intoxication. Electroencephalogram shows depression of waves.

**Thalamus**—Not analgesic. Large doses may cause anarthria.

**Eye**—Loss of conjunctival sensitivity and wink reflex.

**Pharynx**—"Gag" reflex reduced by large doses.

**Lungs**—Respiration slowed as in normal sleep.

**Heart**—No significant action.

**Kidney**—Eliminates bromide ion and chloride ion in same ratio as it exists in plasma. Bromism causes depletion of chloride ion.

**Blood Pressure**—Not affected. May reduce if elevated from psychic causes.

**Gastrointestinal Tract**—Irritated mucosa may cause nausea. Readily absorbed and distributed like  $\text{Cl}^-$  ion.

**Gonads**—Sex instinct depressed by large doses.

**Reflexes**—Reduced. Peripheral sensory organs stupefied.

**Tissues**—Bromide ion indifferent to most tissues except brain. Body does not differentiate between chloride and bromide ions.

**Stim**—Beats frequent.

**DOSE**—1-2 grams. Single doses of no value. Cumulative action results in "bromism" if administered over prolonged period.

**PREPARATION**—Used as salt of potassium, sodium, calcium or ammonia. A mixture known as triple bromide may be used. Potassium bromide is included in the U.S.P.

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

## MAGNESIUM ION

The magnesium ion occurs in aqueous solutions of soluble salts of magnesium. Magnesium is a normal constituent of blood and other tissues. High concentrations in blood depress the central nervous system.

**Cerebrum**—Depresses if administered parenterally. Mild at 10 mgm.-% in serum. Anesthesia at 20 mgm.-%  
Reversed by calcium intravenously

**Respiration**—Paralyzed by large parenteral doses. Falls before circulation.

**Gallbladder**—Hypertonic solutions injected into duodenum increase flow of bile.

**Kidney**—Ion easily and rapidly eliminated after oral ingestion. In presence of renal disease excretion impaired. Toxic amounts may cause depression stimulating uremia.

**Blood**—Normally present in 2-3 mgm.-% 80% ionized and diffusible; remainder bound to proteins. Concentration in red cells higher than serum.

**Skin**—Used as compresses in hypertonic solution in infections to dehydrate area.

**Card**—Induces spinal analgesia if administered intrathecally. Depressed when large amounts are administered intravenously.

**Heart**—Depresses to heart muscle. High concentrations cause bradycardia, arrhythmias and cardiac arrest. Action antagonized by calcium.

**Blood Pressure**—Falls after toxic doses.

**Gastrointestinal Tract**—Absorbed with difficulty. Oral doses do not raise serum level. Absorption enhanced by acid reaction in intestine; retarded by alkaline. Causes withdrawal of water and catharsis.

**Muscle**—Possesses a curare-like action. Excitation of striated muscle by nerve impulses prevented. Present in high concentration— $\approx 1$  mgm.-% in muscle cells.

**Nerve**—High concentrations locally applied block conduction. Concentration necessary too high for safety.

**PREPARATION**—Used as the sulphate. 10 cc. of a 25% solution intramuscularly for adults or 8 cc. of a 25% per 20 lbs. body weight. Two per cent solutions are isotonic.

### USES

Control convulsions caused by encephalopathies. Action augmented by morphine, ether and other central nervous system depressants. Used with rectal ether and morphine.

### ADMINISTRATION

Usually administered intramuscularly. Local anesthetic effect inhibits mass pain of cataplexy.

## SECTION VIII. ALIPHATIC NONVOLATILE AGENTS

### ETHYL ALCOHOL

**PROPERTIES**—Ethyl alcohol is a colorless, mobile, inflammable fluid possessing a burning taste and pleasant odor. Absorbs water from air. S.G. 0.798 at 15°C. B.P. 78.5°C. Solidifies below -130°C. Flash point between 9 and 11°C. Formula  $C_2H_5OH$ . M.W. 46.05. Made by fermentation of starches and synthetically from acetylene or ethylene. Also known as ethanol or hydroxy ethane.



**PREPARATION**—Anhydrous, absolute or 100% for nerve blocking. Alcohol U.S.P. 92.5% by weight or 94.9% by volume. Alcohol, diluted U.S.P. 49.0% by volume. Alcohol and dextrose—5% alcohol and 5% dextrose in distilled water for intravenous administration.

**Brain and Cord**—Irregular descending depression. Never a stimulant. General anesthesia results after unconsciousness is established. Brain absorbs drug. Brain level reaches peak after blood level.

**Distribution in Tissues**—Passes into all tissues and body fluids. Concentration in brain and spinal fluid rises and falls at a slower rate than in other tissues.

**Tolerance**—Tolerance develops after repeated use. Cross tolerance is allied. Aliphatic anesthetics and hypnosis, etc. occurs. Addiction may occur after prolonged continued use, particularly in individuals having psychopathic personality.

**Fate**—Small amounts completely oxidized. Large amounts cause appearance of intermediate products (aldehydes, acetic acid) which appear in breath and urine. Approximately 10 cc. oxidized per hour. Oxidation accelerated by glucose and insulin. Alveolar air concentration of 1 mgm. per liter indicates intoxication.

**Sensory Nerve**—Temporarily destroyed by 80% concentration. Nerve fibers regenerate in due time. Varies upon size and degree of destruction and the nerve.

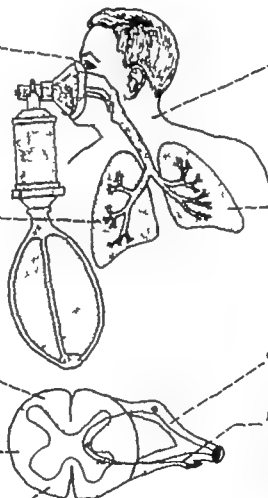
**Cell Body and Ganglia**—Attacked and destroyed.

**Motor Nerve**—Requires more concentrated solution for destruction than sensory or autonomic nerve fibers.

**Perineural Injection**—Five cc. absolute alcohol into soft tissue causes an area of necrosis 1 cm. in diameter. Histologic degenerations of nerve similar to that obtained when nerve is sectioned. Similar to Wallerian degeneration. Neuritis and sclerosis follows.

**Autonomic Nerve Fibers**—Destroyed with same efficacy as sensory nerves.

**Bactericidal Action**—80 to 90% kills non-sporulating bacteria. 70% most effective; 88% not as effective as more dilute solutions.





# THE PHARMACOLOGY OF ANESTHETIC DRUGS

60

**Cerebrum**—Depressed. Ability to concentrate and discriminate are diminished. Memory and insight dulled. Behavior depends upon the personality of individual, tolerance to drug and presence of extraneous stimuli.

**Temperature Regulating Center**—Depressed especially with large doses.

**Medulla**—Depressed. Anesthetic dose and dose necessary to cause respiratory failure close to each other. Possesses a narrow margin of safety.

**Vasomotor Center**—May be depressed, causing vasodilatation.

**Respiratory Center**—Narcotic doses depress. Small doses have no effect. Intoxicating doses paralyze centers.

**Lungs**—No remarkable effects. May be absorbed from pulmonary alveoli if vaporized. 0.5 to 8% may be eliminated here. Not a chief avenue of elimination. Respiration is stimulated by small doses reflexly. Ordinary doses do not affect ventilation. Minute volume exchange decreased during marked intoxication.

**Bronchioles**—Unaffected.

**Muscle**—Decreased only when large amounts are injected and sleep follows. Acts as substitutes for carbohydrates.

**Liver**—Depresses liver function. Dye excretion impaired causes depletion of glycogen. Inhibits reconversion of lactic acid to glucose. Prolonged continued use may cause parenchymal damage if pre-existing liver disease is present. Drug oxidized here.

**Bile**—Minute amounts excreted into bile.

**Kidney**—No pathological effect on normal kidneys. Induces diuresis. 9 to 10% may be eliminated unchanged into urine. Amount in urine varies with volume.

**Uterus**—No significant effects.

**Genitalia**—Possesses no aphrodisiac power. May decrease sexual power.

**Arteries**—General depression of reflex activity follows intoxicating doses. Reflex activity depressed.

**Body Temperature**—Falls due to increased heat loss from dilatation of cutaneous vessels and depression of temperature regulating center.

**Intracranial Pressure**—Not altered unless blood pressure falls. Prolonged increase of secretion of spinal fluid may be cause of cerebral edema in chronic alcoholism.

**Eye**—Reflexes disappear only after massive doses.

**Mucosa**—May cause irritation and inflammation when applied locally.

**Pharynx**—Hyperemia results if applied locally.

**Salivary Gland**—Usually stimulated. Flow of saliva increased.

**Larynx**—No effect.

**Heart**—No direct cardiac stimulation. Small doses increase pulse rate. No direct effect on myocardium sufficiently. Toxic doses depress. Distention of coronary vessels.

**Blood Pressure**—Systolic pressure rises and diastolic falls with small doses. Large doses lower systolic and elevate diastolic. Toxic doses depress vasomotor center causing hypotension.

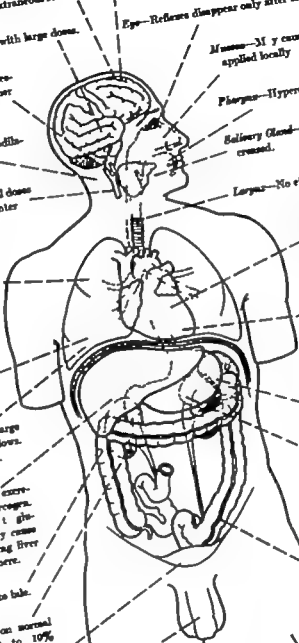
**Venous Pressure**—No effect. Thrombosis of veins in intravenous use.

**Stomach**—Oral ingestion causes hyperemia of gastric and intestinal mucosa. Reflexly stimulates secretion by reflex action. 10% solution causes secretion of jejunum rich in sodium but poor in pepsin. No effect on succus acidus. Above 30% secretion may be delayed. Above 50% secretion may be delayed. Alcohol used as solvent for drugs (ethers) may stimulate absorption of all substances from gastrointestinal tract.

**Intestine**—Approximately 80% absorbed here. Rate of absorption varies with concentration. Rapidly absorbed from small bowel. No effect on intestinal digestion. May be absorbed through colonic mucosa.

**Muscle**—No increase in muscular activity. Relaxed in overintoxication.

**Skin**—No absorption through skin. Locally applied causes cooling by evaporation. Rubbing causes counter irritation and rubefaction action. Hardens on repeated application. Cutaneous vessels dilated by large oral doses causing flushing.



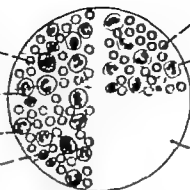
## BLOOD

Oxygen Content—Unchanged in arterial blood unless severe depression of respiration occurs.

Oxygen Capacity—Unchanged.

Lactic Acid—Increased.

Glucose—Unchanged. May increase in severe intoxication.



Carbon Dioxide Content—Unchanged. May be slightly elevated.

Carbon Dioxide Combining Power—Unchanged. May be decreased slightly in mild intoxication and increased in deep.

Blood Concentration—Peak reached after first hour in single administration. Plasma contains twice as much as corpuscles. 200 mgm.% usually indicates mild or moderate intoxication, 300 mgm. intoxication, 400 mgm. advanced intoxication. 500–600 mgm. is fatal concentration. Concentration required to cause intoxication varies from one individual to next. Traces remain in blood for as long as 24 hours. Work does not influence blood levels.

## USES

- (1) As a solvent for drugs for oral use (elixirs)
- (2) As a bactericide locally applied.
- (3) For interrupting nerve fibres (by local or intraspinal injection)
- (4) As a hypnotic and sedative by oral or intravenous route
- (5) To secure vasodilatation in peripheral vascular disease.

## CONTRAINDICATIONS AS A HYPNOTIC OR ANESTHETIC

- (1) Hepatic and renal disease
- (2) Urinary tract infection
- (3) Ulcerations of gastrointestinal tract.

## ADVANTAGES

None as an anesthetic.

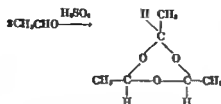
## DISADVANTAGES AS A HYPNOTIC OR ANESTHETIC

- (1) Anesthetic concentration is close to the lethal concentration.
- (2) Response varies from subject to subject.
- (3) Onset of narcosis variable and often delayed.
- (4) Duration of action variable.
- (5) Non-controllable
- (6) Causes sloughs and necrosis when injected locally
- (7) Causes thrombosis of veins when used intravenously

## PARALDEHYDE

**HISTORY**—Introduced by Cervello in 1882. Intravenous use reported by H. Noel and H. S. Sontar in 1913.

**PREPARATION**—By interaction of acetaldehyde and concentrated sulphuric acid. Three molecules of the aldehyde polymerize to form one molecule of paraldehyde. Empiric formula is  $(\text{CH}_3\text{CHO})_3$ . Structural formula is



**Cerebrum**—Depressed. Excitomotor and delirious uncommon. Not analgesic. Restlessness when administered in presence of pain. Large doses may cause sleep in presence of pain. Few or no after effects.

**Vasomotor Center**—No effect in sedative doses. Depressed during deep hypnosis.

**Cerebellum**—Remains active. Depressed during deep hypnosis.

**Respiratory Center**—Depressed by large doses. Respiratory failure precedes circulatory failure.

**Vomiting Center**—Not stimulated.

**Carotid Sinus**—Carotid sinus mechanism remains active.

**Lungs**—Respiratory rate increased in light hypnosis, decreased in deep. Amplitude decreased, mucous volume exchange decreased. Hering-Breuer reflex intact. Epithelial lining irritated. Drug (11-23%) exhaled from the lung unchanged.

**Liver**—Unaltered results not reported. Up to 80% oxidized here.

**Kidney**—Oliguria in deep hypnosis. Oliguria may follow in recovery period. Drug excreted in urine; concentration parallels plasma level.

**Skeletal Muscles**—N. effect in hypnotic doses. Relaxed in deep hypnosis. Relaxation not satisfactory for major surgery.

**Reflexes**—Superficial and deep remain active during sedation. Obviated by deep hypnosis. Knee and ankle jerk remains active in deep hypnosis.

**Body Temperature**—No notable effect. Decreased 1 to 2°F in deep hypnosis.

**Eyes**—No notable effect during sedation. Pupils dilated and eyeball movements abolished in deep hypnosis.

**Mucous Membranes**—Irritated locally causing copious secretion of mucus.

**Pharynx**—"Gag" reflex abolished in deep hypnosis.

**Larynx**—Cough reflex abolished during deep hypnosis. Remains active during light hypnosis and sedation.

**Salivary Glands**—Stimulated at first due to local irritation. Depressed during deep hypnosis.

**Heart**—N. significant effect during sedation or hypnosis. Rate slightly increased. Rhythm not altered. Circulation time prolonged in deep hypnosis. Massive doses depress the myocardium.

**Blood Pressure**—No significant changes during sedation or mild hypnosis. Falls during deep hypnosis or overdose.

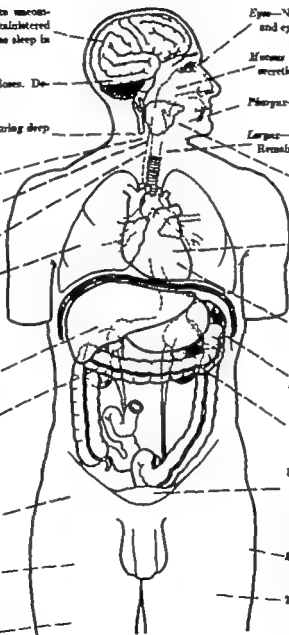
**Spleen**—Contracted during deep hypnosis. N. significant effect during sedation.

**Gastrointestinal Tract**—Inhibition of movements in deep hypnosis.

**Uterus**—Contraction of the intact organ not increased by hypnosis doses. May be decreased during deep hypnosis. Drug passes through placenta to fetus causing depression of fetal respiration.

**Skin**—Temperature decreased. Slight trace in perspiration.

**Tissues**—Drug distributed uniformly to all tissues, muscle, heart, kidney, liver and brain. Cumulative action may follow repeated use.



## BLOOD

**Red Cells**—Hemococentration during deep hypnosis. Causes hemolysis when administered intravenously.

**Sedimentation Rate**—Unchanged.

**Bleeding Time**—Unchanged.

**Clotting Time**—Unchanged.

**Oxygen Capacity**—Increased during deep hypnosis. Content reduced during deep hypnosis from respiratory depression.

**Blood Sugar**—Unchanged during sedation. Increased during deep hypnosis.

**Carbon Dioxide Combining Power**—Reduced during deep hypnosis.

## PROPERTIES

Clear, colorless, mobile liquid, possessing a pungent odor. Odor clings to surrounding objects for days. Specific gravity 0.969 at 20°C. Boiling point 18°C. Burns when ignited. Solubility 1:1 in ether at 20°C. Highly soluble in fats and alcohol. Acids decompose it to acetaldehyde. Self-sterilizing and remains sterile. Does not possess chemical reactions of aldehydes. Included in the U.S.P. XIII.

**Impurities**—Acetaldehyde, ethyl alcohol, acetic and other organic acids. Stable under ordinary circumstances.

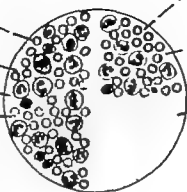
**Storage**—In dark bottles. Protected away from light, heat and air.

## USES

- (1) As hypnotic, particularly in chronic alcohol addicts and mentally disturbed patients.
- (2) As basal narcotic preliminary to surgery.
- (3) As rectal analgesic and anesthetic for obstetrics.
- (4) As anti-convulsant.
- (5) As solvent for other drugs—barbiturates.

## CONTRAINDICATIONS

- (1) Broncho-pulmonary disease—exacerbated by lungs.
- (2) Hepatic and renal insufficiency.
- (3) Gastro-intestinal disease irritates mucosa.



## ADMINISTRATION

**Orally**—For hypnosis, 5 cc. with flavoring. **Rectally**—For hypnosis, 15 to 30 cc. in equal volume of saline (often used with 1 cc. benzyl alcohol to avert local irritating effects). **Intravenously**—For rapid sedation 5 to 10 cc. (deep hypnosis lasts several minutes, followed by sleep lasting an hour or more). Not recommended for surgical anesthesia.

**Tolerance**—Habituation uncommon. Cross tolerance develops between it and alcohol and aliphatic hypnotics. Addiction uncommon.

## ADVANTAGES

None. Erroneously considered safe hypnotic with wide margin of safety.

- (1) Sleep sets in promptly (10-15 minutes). Resembles normal sleep. Lasts 5 to 6 hours.
- (2) No after effects.
- (3) Delirium uncommon.
- (4) Prompt onset of action.

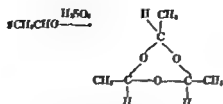
## DISADVANTAGES

- (1) Possesses an unpleasant odor and is disagreeable.
- (2) Variability of action.
- (3) Lack of analgesic power.
- (4) Narrow margin of safety in large doses.
- (5) Irritates mucosa of mouth, stomach or rectum.
- (6) Basal hypnosis disturbs metabolism. Possibility of tolerance and addiction.

## PARALDEHYDE

**HISTORY**—Introduced by Cervello in 1882. Intravenous use reported by H. Noel and H. S. Sontar in 1913.

**PREPARATION**—By interaction of acetaldehyde and concentrated sulphuric acid. Three molecules of the aldehyde polymerize to form one molecule of paraldehyde. Empirical formula is  $(CH_3CHO)_3$ . Structural formula is



**Cortex**—Depressed. Excitement and delirium uncommon. Not analgesic. Restlessness when administered in presence of pain. Large doses may cause sleep in presence of pain. Few or no after effects.

**Ischemic Crises**—No effect in sedative doses. Depressed during deep hypnosis.

**Cough Crises**—Remains active. Depressed during deep hypnosis.

**Respiratory Crises**—Depressed by large doses. Respiratory failure precedes circulatory failure.

**Vomiting Crises**—Not stimulated.

**Cerebral Strain**—Cerebral mechanism remains active.

**Lungs**—Respiratory rate increased in light hypnosis, decreased in deep. Amplitude decreased, minute volume exchange decreased. Hering-Breuer reflex intact. Epithelial lining irritated. Drug (11-45%) exhaled from the lung unchanged.

**Liver**—Unfavorable results not reported. Up to 80% excreted here.

**Kidney**—Oliguria in deep hypnosis. Diuresis may follow in recovery period. Drug excreted in urine concentration parallels plasma level.

**Skeletal Muscles**—No effect in hypnotic doses. Relaxed in deep hypnosis. Relaxation not satisfactory for major surgery.

**Reflexes**—Superficial and deep remain active during sedation. Obstained by deep hypnosis. Knee and ankle jerk remain active in deep hypnosis.

**Body Temperature**—No notable effect. Decreased 1 to 2°F in deep hypnosis.

**Eyes**—No notable effect during sedation. Pupils dilated and eyelid movements abolished in deep hypnosis.

**Mucous Membranes**—Irritated locally causing copious secretion of mucus.

**Pharynx**—"Gag" reflex abolished in deep hypnosis.

**Larynx**—Cough reflex abolished during deep hypnosis. Remains active during light hypnosis and sedation.

**Salivary Glands**—Stimulated at first due to local irritation. Depressed during deep hypnosis.

**Heart**—No significant effect during sedation or hypnosis. Rate slightly increased. Rhythm not altered. Circulation time prolonged in deep hypnosis. Massive doses depress the myocardium.

**Blood Pressure**—No significant changes during sedation or mild hypnosis. Falls during deep hypnosis or overdose.

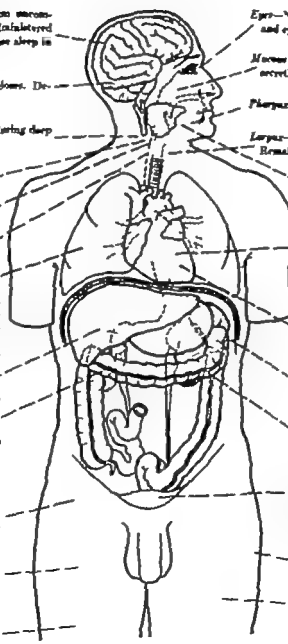
**Spleen**—Contracted during deep hypnosis. No significant effect during sedation.

**Gastrointestinal Tract**—Inhibition of movements in deep hypnosis.

**Uterus**—Contraction of the intact organ not increased by hypnotic doses. May be decreased during deep hypnosis. Drug passes through placenta to fetus causing depression of fetal respiration.

**Skin**—Temperature decreased. Night trace in perspiration.

**Tissues**—Drug distributed uniformly in all tissues, muscle, heart, kidney liver and brain. Convulsive action may follow repeated use.



## BLOOD

**Red Cells**—Hemoconcentration during deep hypnosis. Causes hemolysis when administered intravenously.

**Sedimentation Rate**—Unchanged.

**Bleeding Time**—Unchanged.

**Clotting Time**—Unchanged.

**Oxygen Capacity**—Increased during deep hypnosis. Contrast reduced during deep hypnosis from respiratory depression.

**Blood Sugar**—Unchanged during sedation. Increased during deep hypnosis.

**Carbon Dioxide Containing Power**—Reduced during deep hypnosis.

## PROPERTIES

Clear colorless, mobile liquid, possessing pungent odor. Odor clings to surrounding objects for days. Specific gravity 0.800 at 20°C. Boiling point 16°C. Burns when ignited. Solubility 1:1 in water at 20°C. Highly soluble in fats and alcohol. Acids decompose it to acetaldehyde. Will sterilizing and remains sterile. Does not possess chemical reactions of aldehydes. Included in the U.S.P. XIII.

**Impurities**—Acetaldehyde, ethyl alcohol, acetic and other organic acids. Stable under ordinary circumstances.

**Storage**—In dark bottles. Protected from light, heat and air.

## ADMINISTRATION

**Orally**—For hypnosis, 5 cc. with Barbitone. **Rectally**—For hypnosis, 15 to 30 cc. in equal volume of saline (often used with 1 cc. barbitone alcohol to alleviate local irritating effects). **Intravenously**—For rapid sedation 5 to 10 cc. (deep hypnosis lasts several minutes, followed by sleep lasting an hour or more). Not recommended for surgical anesthesia.

**Tolerance**—Habituation uncommon. Cross tolerance develops between it and alcohol and aliphatic hypnotics. **Addiction** uncommon.

## ADVANTAGES

None. Extensively considered a safe hypnotic with wide margin of safety.

- (1) Sleep sets in promptly (10-15 minutes). Resembles normal sleep. Lasts 5 to 6 hours.
- (2) No after effects.
- (3) Delirium uncommon.
- (4) Prompt onset of action.

## DISADVANTAGES

- (1) Pungent as unpleasant odor and is disagreeable.
- (2) Variability of action.
- (3) Lack of analgesic power.
- (4) Narrow margin of safety in large doses.
- (5) Irritates mucosa of mouth, stomach or rectum.
- (6) Basal hypnosis disturbs metabolism. Possibility of tolerance and addiction.

## CONTRAINDICATIONS

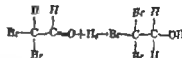
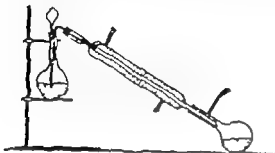
- (1) Broncho-pulmonary disease—exacerbated by lungs.
- (2) Hepatic and renal insufficiency.
- (3) Gastro-intestinal diseases—irritates mucosa.

## TRIBROMPHTHANOL (AVERTIN)

**HISTORY**—Produced by Willstätter and Dujberg in Germany in 1923. First used as an anesthetic by F. Eicholtz in man and animals in 1926. Clinical use promoted by Butzenberger in 1927. Studied pharmacologically by Straub in 1928. Intravenous use reported by Martin Kirschner in 1929.

**SYNONYMS**—Bromethol Nectanol, Ethobrom E 107

**PREPARATION**—Tribromacetalddehyde (Bromal) is first formed by treating ethyl alcohol with bromine. The bromal is then reduced with aluminum ethoxide in an atmosphere of nitrogen.

**PREPARATION**

Crystals. Packed in sealed dark ampoules available for local application or intravenous use.

**Avertin Fluid**—Clear somewhat amber heavy fluid, packed in dark bottle. Specific gravity 1.4 (20°C), sweet, camphor-like odor. Amylene by dist. volatiles causing precipitation of crystals.

**PROPERTIES**

**Physical**—White crystalline powder possessing ethereal odor. Melting point 80°C. Sublimes with decomposition. Poorly soluble in water. Soluble in organic solvents. Very soluble in amylen hydrat. 3.7 grams dissolve per 100 cc. H<sub>2</sub>O at 37°C.

**Chemical**—Not stable. Decomposes easily yielding dibromacetalddehyde and hydrocyanic acid. Decomposition partly (red, blue, light blue) and small. Decomposition detected by addition of indicator (Congo Red) which turns purple due to presence of acid.



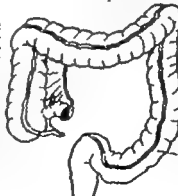
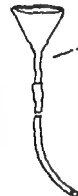
**Avertin Fluid**—Tribromophthanol plus amylen hydrate yields "Avertin Fluid." Included in U.S.P. VIII.

**ADMINISTRATION**

Used rectally as basal anesthetic (hypnotic). Also used locally as an antipruritic, particularly in urethral spaces. When used intravenously it causes short, variable action, followed by prolonged hypnosis. Not suitable orally because of irritation to mucous membranes and decomposition as it passes through stomach.

**METHOD**

Three per cent. Avertin fluid in pure water at 37°C. by rectum, one-half hour pre-operatively. Average dose 60 to 80 mgm. per kilogram. Maximum total volume 0.1 to 0.2 cc. for females 0.1 to 0.2 cc. for males. Childrens tolerance and require larger doses, approximately 100 mgm. per kilo. Doses causing complete anesthesia (130 to 200 mgm. kilo) cause marked depression, often fatal. Administer to patient on left side. Requires complementary stimulation on regional anesthetics because reflexes are not completely abolished. Surgical anesthesia is not obtained except with dangerous dosages.



**Absorption**—Variable—80% absorbed from colon in first 10 ml. after 80% absorbed in first 20 minutes. 80% absorbed in first 25 minutes. None absorbed from small bowels. Absorption from small intestine more rapidly than large. Onset of hypnosis more rapid if water is present. Sometimes much occurs shortly after administration. No contraindications to success unless decomposed. 31 y. cause proctitis following repeated administration.

**Duration of Hypnosis**—With 80 mgm. per kilo, 25% last less than 1 hour. Average duration 91 hours. Gradual emergence with drowsiness. Emetic reflex in post-operative period due to presence of pain.

**Blood Concentration**—0.1 to 10 mgm. per 100 cc. of blood results in sleep. Analgesia occurs when drug concentration has fallen to 2 to 3 mgm. per 100 cc.

**Fluorescence**—Concentration in the heart parallel blood, lipid and nervous tissue absorb it rapidly and contract it after disappearance from blood. Kidney may contain as much as nerve tissue. Circulation effect follows repeated administration.

**Excretion**—Conjugated in liver with glycolic acid. Product excreted in urine 70 to 80% detoxified and eliminated in two to four hours. None eliminated via lungs or intestines. Conjugated product does not possess hypnotic properties. Any less hydrate eliminated unchanged through lungs and kidney. Detoxification and elimination delayed in presence of liver or renal disease. Exogenous glycolic acid does not hasten destruction.

**Cortex**—Depressed. Lower cortical afferent pathways intact. Not an analgesic. Painful stimuli rouse patient in light hypnosis.

**Temperature Regulating Center**—Depressed. Body temperature falls.

**Cough Center**—Completely depressed by massive doses only. Reflex present, partly active even in deep hypnosis.

**Vasomotor Center**—Depressed. Blood pressure falls at onset of hypnosis.

**Emetic Center**—Depressed. Nausea and vomiting uncommon.

**Respiratory Center**—Depressed. Threshold to  $\text{CO}_2$  stimulation raised. Overdosage results in respiratory failure.

**Lungs**—Slight increase in respiratory rate and decrease in amplitude of respiratory movements resulting in a decreased minute volume exchange. Hering-Breuer reflex remains active. No effect on alveoli. Bronchial musculature relaxed. Bronchial cough reflex remains active.

**Diaphragm**—Movements decreased in deep hypnosis.

**Mriahum**—Decreased on average of 12%.

**Adrenal**—No significant effect. Epinephrine contract unchanged. Necrosis of adrenals in overdosage reported.

**Gallbladder**—Volume of bile flow increased. Bile ducts empty unchanged.

**Liver**—Excretion of bromobenzole impaired. Glycogen depleted. Output of bile salts reduced. Drug detoxified here by conjugation with glucuronic acid. Cloudy swelling only pathological change occurring (never like chloroform). Hepatitis uncommon.

**Kidney**—Azotemia or oliguria during narcosis followed by polyuria afterward. Conjugated product eliminated in urine. Water diuresis normal after narcosis.

**Uterus**—Relaxation of muscle follows local application.

**Venae**—Superficial and deep reflexes remain active in mild hypnosis. Disappear after large dose in deep hypnosis.

**Sphincters**—Not relaxed except in deep hypnosis unless drug is decomposed or by repeated use.

**Body Temperature**—Falls due to decreased metabolic rate. Depression of center and increased heat loss due to relaxation of skin vessels.

**Intracranial Pressure**—Decreased if no anoxia is present or during hypotension. Unchanged otherwise. Concentration in spinal fluid one-half that of blood. Spinal fluid pressure decreased.

**Pial Vessels**—Constricted.

**Hypothalamus**—Depressed.

**Eyes**—Lid reflex disappears. Pupils constricted. Eyeballs fixed or movements sluggish. Intracranial tension decreased. Tear secretion reduced. Corneal reflex abolished in deep hypnosis.

**Salivary Glands**—Depressed. No secretion of saliva.

**Mucous Membranes**—Not affected. Ciliary activity decreased. Mucus secretion, slight or abolished.

**Pharynx**—"Gag" reflex not abolished. Tongue sufficiently relaxed to cause obstruction during paroxysms. Trace of amylase hydrate in breath.

**Thyroid**—Resistance to drug increased by administration of thyroxine 24 hours prior to administration of drug.

**Larynx**—Cough reflex obtunded but not abolished.

**Heart**—Rate increased. Cardiac output decreased. Rhythm slightly changed. EKG changes are insignificant. Large doses depress myocardium and decrease cardiac output, dilatation of coronaries in perfused heart. Does not sensitize heart to epinephrine.

**Blood Pressure**—Changes occur early (15 min. average). Decrease of 80% or more due to depression of vasomotor center and peripheral vascular dilatation. Systolic falls, diastolic little changed.

**Venous Pressure**—Decreased. May increase in deep hypnosis.

**Spleen**—Effects not studied. Probably constricted.

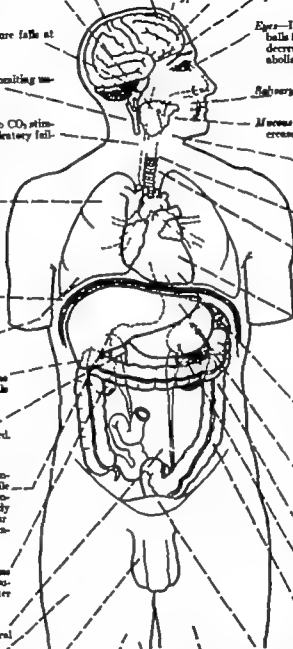
**Stomach**—Motility decreased or abolished by large doses.

**Intestines**—Motility reduced or abolished by large doses.

**Uterus**—Contractions of pregnant uterus decreased in force and frequency. Atony and relaxation follows large dose. Drug passes through placenta to fetus depressing respiration. Recovery of infant delayed as long as one week.

**Skin**—Temperature increased due to dilatation of skin vessels. Brownish recovered in sweat. Drug in alcoholic solution absorbed through skin.

**Skeletal Muscles**—Relaxed with large doses.





**Total Blood Volume**—Decreased.

**Red Blood Cells**—Increased in number. Total hemoglobin increased. No change in morphology of cells. Sedimentation rate decreased.

**Leukocytes**—Total increased. Polymorphonuclears increased relatively and absolutely in first 24 hours. No change in morphology. Phagocytosis decreased in deep narcosis.

**Platelets**—Decreased as much as 75% after 30 minutes of narcosis.

**Oxygen Capacity**—Slightly increased due to bromoconcentration. Oxygen content unchanged in arterial blood unless respiratory depression occurs.

**Carbon Dioxide**—Total content increased.

**Carbon Dioxide Combining Power**—Decreased. Returns to normal within 48 hours. Total base decreased. Bicarbonate increased at first, decreased after 30 minutes. pH increases 0.1 to 0.2 units during narcosis.

**Bleeding Time**—Decreased due to hypotension. Capillary ooze minimal.

**Clotting Time**—Increased as much as three minutes.

#### URINE

Specific gravity increased. Volume decreased during and increased after narcosis. Total 24-hour volume decreased. Non-protein nitrogen decreased during and increased after narcosis. Phosphates increased, maximum in 6 hours. Albumin present in 60% of cases. Detoxified product excreted in urine.

#### USES

- (1) As "broad narcosis" (in conjunction with other forms of anesthesia—inhalation or regional) for apprehensive patients.
- (2) To control hyperirritable states of central nervous system manifested by convulsions.
- (3) As bronchodilator in asthmatic states.
- (4) For intracranial surgery.
- (5) As an antispasmodic.

#### ADVANTAGES

- (1) Reduces metabolic rate and reflex irritability.
- (2) Rapid onset on induction of narcosis.
- (3) Gradual recovery resulting in prolonged amnesia.
- (4) May be administered at bedside to allay preoperative apprehension.
- (5) Eliminates excitement during induction of inhalation anesthesia.
- (6) Non-irritating to respiratory tract.
- (7) Post-operative nausea and vomiting decreased.
- (8) Reduces amount of inhalation anesthetic.
- (9) Reduces intracranial pressure.

**Plasma Volume**—Decreased.

**Calcium**—Unchanged.

**Bicarbonate**—Reduced.

**Phosphates**—Total phosphates increased during recovery.

**Chloride**—Unchanged.

**Glucose**—80% increase within first 30 minutes with a continued rise thereafter. Derived from liver glycogen which is depleted.

**Non-protein Nitrogen**—Increased during narcosis. Returns to normal within 24 hours. Gradually falls after recovery.

**Urea**—Decreased during narcosis. Returns to pre-narcotic level during recovery.

**Lipids**—No significant change. Slight increase in total cholesterol. No change in cholesterol ester content.

**Sile Salts and Electrolytes**—Slightly decreased plasma level.

**Ketones**—Appear after narcosis.

**Pathology**—No definite pathological changes attributable to drug.



#### CONTRAINDICATIONS

- (1) Hepatic or renal disease.
- (2) Any "toxemia" or sepsis or acidosis from any cause.
- (3) Shock or other forms of hypotension.
- (4) Dehydration.
- (5) Low basal metabolic rate (hypothyroidism).
- (6) Chronic pulmonary disease.
- (7) Enteritis, colitis, neoplasms of colon.
- (8) Old age.
- (9) Anemia.
- (10) Chronic alcohol addicts.

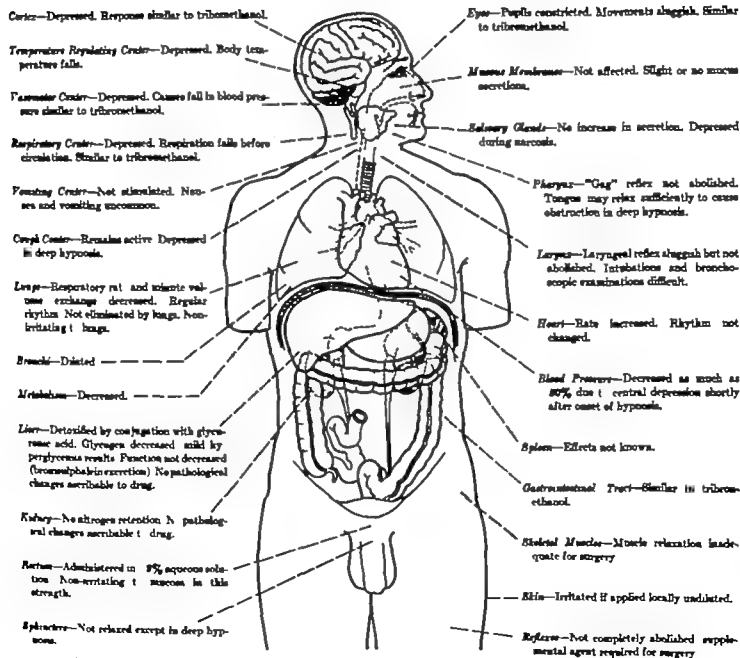
#### DISADVANTAGES

- (1) Non-contraindicable—since given dose is administered it cannot be retrieved.
- (2) Must be detoxified for elimination.
- (3) Dose difficult to estimate due to variations in susceptibility and absorption from rectum.
- (4) Not an analgesic—supplemental anesthetic agent necessary to complete surgical procedures.
- (5) Respiratory depression common.
- (6) Hypotension frequent.
- (7) Repeated doses result in cumulative effects.
- (8) Laryngeal and pharyngeal reflex not abolished.
- (9) Requires constant attendance by expert individual during period of narcosis.
- (10) Not chemically stable—decomposed solutions cause rectal and colonic irritation.

## TRICHLORETHANOL

**HISTORY**—Introduced by Kauls in 1882. Molitor reinvestigated its pharmacological properties in 1937. Used clinically by Wood in the United States in 1938. Also known as Ethapon.

**CHEMICAL PROPERTIES**—Clear colorless liquid specific gravity 1.55 (20°C) 8.8% solubility in water at 20°C boiling point 151°C. at 737 mm Hg. Not flammable. Sweet smelling, stable. Decomposes at temperatures above 40°C. Onset of narcosis irregular. Duration one to five hours. Amylene hydrate not required. Chemical structure as follows



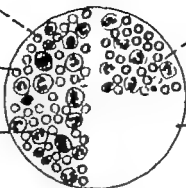
Trichlorethanol differs from tribromethanol in having three chlorine atoms in place of the bromine atoms. Pharmacologically they are similar. Trichlorethanol possesses a somewhat wider margin of safety but a milder potency.

*Oxygen Content*—No decrease in arterial blood.

*Glucose*—Slight rise.

*Bleeding Time*—Unchanged.

*Clotting Time*—Unchanged.



*Carbon Dioxide Combining Power*—Decreased.

## USES

Same as for tribromethanol.

## INDICATIONS

Same as for tribromethanol.

## METHODS OF ADMINISTRATION

*Rectally*—Same as for avertin.

*Intravenously*—Not useful or recommended.

*Orally*—Similar to tribromethanol—not suitable.

## CONTRAINDICATIONS

Same as for tribromethanol.

## ADVANTAGES

Similar to tribromethanol in comparison to other hypostic drugs. Superior to avertin as follows:

- (1) It is less expensive.
- (2) It is somewhat more stable chemically.
- (3) It does not require amylase hydrate or other vehicle as a solvent.

*Dose*—100-125 mgm. per kilogram in a 5% solution (aqueous) rectally.

*Onset of Hypnosis*—Approximately 10 minutes after administration.

## DISADVANTAGES

Same as for tribromethanol. Inferior to tribromethanol in the following ways:

- (1) It is less potent.
- (2) Its response and duration of action are more variable.
- (3) Respiratory depression often more profound.
- (4) Dose is estimated with greater difficulty.
- (5) Duration of hypnosis shorter.

*Duration of Hypnosis*—One to two hours when administered rectally.

*Elimination*—Detoxified by conjugation with glycemic acid. Usually eliminated within six hours.

## CHLORAL (TRICHLORACETALDEHYDE)

**HISTORY**—First prepared by Leibig in 1832. Composition determined by Dumas in 1834. Introduced by Liebreich. First drug to be used for intravenous anesthesia by P. Oré in 1875 in France (Lyons).

**CHEMISTRY**—Made by chlorinating and oxidizing ethyl alcohol with chlorine. Forms a hydrate with water.

**PROPERTIES**

**Physical**—Clear, colorless, caustic liquid with a pungent disagreeable odor. Boils at 85° F.G. 1.206 at 25°C.

**Chemical**—Forms hydrate with water which melts at 84° and boils at 96°. Both derivatives very soluble in alcohol, water and ether. Forms alcoholate with ethyl alcohol and chloralose with glucose. Solutions are antiseptic. (Included in U.S.P. XIII.)

**Central**—Depressed. Small doses cause sedation or hypnosis; large doses basal narcosis. Possessors no analgesic action. Hypnotic doses produce sleep from which patient can be awakened.

**Temperature Regulating Center**—Depressed by massive doses. No effect in hypnotic doses.

**Respiratory Center**—Sedative and hypnotic doses have no remarkable effect. Basal narcotic and toxic doses depress. Respiration ceases before circulation.

**Lungs**—No effect. Respiration depressed with basal narcotic doses. Respiratory exchange depressed during hypnosis.

**Branches**—No significant action. Relaxed after basal narcotic doses.

**Metabolism**—Depressed if sleep ensues.

**Liver**—Not affected by hypnotic doses. Hepatitis may follow repeated administration or toxic doses. Liver glycogen mobilized after massive doses causing hyperglycemia.

**Kidney**—Urine flow decreased during basal narcosis. By-product of detoxification (trichloroacetic acid) eliminated by kidney. Albuminuria after toxic doses. Reducing substance excreted into the urine often mistaken for glucose.

**Excretion**—Detoxified in liver by conjugation with glycuronic acid to form trichloroacetic acid (usual dose excreted in 8 to 18 hours).

**Skin**—Locally irritating. Cataplexis venous distended. Skin eruptions may follow use of hypnosis.

**Vasomotor Center**—No effect with sedative and hypnotic doses. May be depressed after massive doses.

**Eyes**—Pupils constricted in deep hypnosis. Reflexes and eye ball movements abolished.

**Pharynx**—Locally irritating.

**Larynx**—No effect. Laryngeal reflex obtained but not completely abolished in deep hypnosis.

**Salivary Glands**—Stimulated by oral ingestion.

**Heart**—Hypnotic doses cause no effect. Massive doses depress myocardium. No notable effect on cardiac rhythm during sedation or hypnosis.

**Blood Pressure**—No effect. Reduced if elevated from psychic stimulation. Toxic doses may depress vasomotor center.

**Stomach**—Absorbed from stomach in part. Irritating to mucosa of gastrointestinal tract. Causes hyperemia, nausea and vomiting from local irritation.

**Intestines**—Rapidly absorbed from intestinal tract. Rapidly absorbed from colon in rectal administration.

**Body Temperature**—Slightly lowered due to heat loss through skin.

**Reflexes**—Unchanged during hypnosis. Depressed during basal narcosis.

**CLINICAL USES**

- (1) As hypnotic alone or in combination with bromides.
- (2) As an anti-convulsant (tetanus, strychnine poisoning, rages, etc.)
- (3) As basal hypnotic and narcotic in pediatrics, surgery and medicine.

**Dose of Hypnosis**—Rectally—10 to 15 minims. Orally 15 to 30 minims. Lasts 6 to 8 hours.

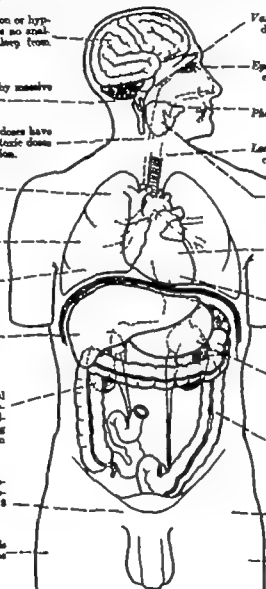
**After Effects**—Very few after effects upon recovery. Tolerance uncommon. Addiction unlikely. No potentiation if administered with ethyl alcohol.

**ADMINISTRATION**

**Orally**—For mild sedation 0.5 to 1 gm. For hypnosis 1 to 2 gm.

**Rectally**—For basal narcosis 2 to 4 gm. Not recommended.

**Intravenously**—Not used.



## LESSER KNOWN ALCOHOLS AND ALDEHYDES

	Amylene Hydrate	Pentyn-ol	Chlorbutanol	Betyl Chloral Hydrate
History	Studied by Harroch and Meyer in 1864.	Introduced in 1901—Barring Corp.	—	Introduced by Liebreich in 1871. Investigated by Aldrich 1918.
Synonyms	Tertiary amyl alcohol. Tertiary pentanol.	Dormicon.	Chlorstane. Acetone chloroform. Methaform.	"Croton chloral hydrate.
Chemical Name	Diisamyl (ethyl carbinol.	3-methyl pentyn-ol 3	Chlorobutol.	Trichlorobutylaldehyde.
Formula	$C_6H_5(C)(CH_3)_2OH$	$CH_3-C \equiv C(CH_3)(OH)-CH_2-CH_3$	$(CCl_3)(C)(CH_2)_2OH$	$CH_3CHCl-CCl_2CHO$
Properties	Colorless volatile liquid B.P. 108°C. Soluble 1 in 3 H <sub>2</sub> O	An unsaturated triple bonded aliphatic alcohol.	Colorless crystals with camphor like odor M.P. 97°C. 1 gm. in 123 CC. H <sub>2</sub> O	Crystalline white powder, pungent odor, acid taste. 1 in 20 H <sub>2</sub> O. Melts at 79°C.
Absorption	From gastro-intestinal tract. Orally 1-2 cc. I.M. 8-4 cc.	From gastro-intestinal tract.	From mucous membrane of G.I. tract.	From gastro-intestinal tract orally and rectally.
Excretion	Into urine. May be conjugated in part in liver.	Into urine. Rapidly eliminated.	Non-volatile. Excreted into urine or detoxified.	Non-volatile. Excreted into the urine or detoxified.
Systemic Effect	Mild hypnotic.	Mild hypnotic. More potent than amylene hydrate.	Depressant used for hypnotic purposes.	Similar to chloral.
Toxicity	Excessive doses depress heart.	Low toxicity.	Large doses depress respiration.	Similar to chloral.
Uses	As hypnotic. Solvent for amylene hydrate. Plays a minor role as hypnotic.	As a hypnotic orally.	Antispasmodic, sedative preservative for parenteral solutions.	As a hypnotic.
Doses	1-4 cc. orally 4-8 cc. rectally	250-500 mgm. orally	0.5-1 gm. orally	0.5-1 gm. orally
Analgesic Effects	None.	None.	Possesses some local anesthetic effect.	Mild analgesic action.
Remarks	Between chloral and paraldehyde in potency.	Low toxicity. Non-cumulative. Antagonized by caffeine.	Depress smooth muscle of G.I. tract. Ineffective in respiratory infections.	May be used externally. More powerful and shorter acting than chloral.

## THE SULPHONE METHANES

The sulphone methanes have been employed for sedation and hypnosis, but because of their feeble action and their tendency to produce cumulative effects are no longer employed. Three of the most important derivatives in this group possess the following properties.

Name	Sulphonal	Trional	Tetronal
History	Introduced by Bauman and Kest in 1893.	Same.	Same.
Properties	Sulphonmethane White bitter powder—slightly soluble in water (1 in 250), melts $+185-186^{\circ}$	Diethyl sulphone ethyl methyl methane White bitter powder. Colorless, odorless crystalline scales. Poorly soluble in water	Diethyl sulphone diethyl methane Bitter white powder. Poorly soluble in water
Action	Hypnotic but not analgesic. Absorbed slowly. Onset one to four hrs. Duration one to five hrs.	Hypnotic but not analgesic.	Hypnotic but not analgesic.
Elimination	Cumulative action results. Excreted partly as ethyl sulphonio acid and partly unchanged in urine. Excreted slowly	More rapidly absorbed and therefore more prompt in its action than sulphonal. Excreted slowly in urine. Cumulative action follows repeated administration.	Slower in onset than sulphonal because of slower absorption. Excreted slowly into urine. Cumulative action follows repeated administration.
Toxic Effects	Large doses depress respiration and circulation		Large doses depress circulation and respiration.
Dose	Dose 1 gm. orally	Dose 1 gm. orally	Dose 1 gm.
Use	As sedative and hypnotic. Used as a hypnotic formerly. Rarely used today	As a sedative and hypnotic. Used as a hypnotic formerly. Rarely used today	As a sedative and hypnotic. Same as sulphonal but slower in action because it is less soluble in water

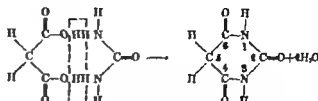
# SECTION IX BARBITURATES AND OTHER NONVOLATILE AGENTS

## BARBITURATES

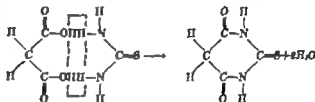
**HISTORY**—Barbital prepared by Fischer and von Mering in 1903 phenobarbital by Hoerlein in 1911 Sponke began to prepare higher molecular weight derivatives in 1916 Since then many chemists have added new compounds.

### CHEMISTRY OF BARBITURATES

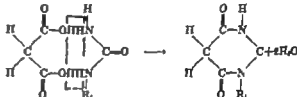
**Chemistry**—Barbiturates are cyclic triazoles composed of a pyrimidine nucleus resulting from a condensation of urea and malonic acid. The resulting malonyl urea (barbituric acid) is non-hypnotic. Replacement of the two hydrogens on carbon 5 by various radicals produces a myriad of central nervous system depressants.



**Thio-barbiturates**—Made by condensing malonic acid with thiourea. Possess similar configuration to barbituric acid except one oxygen atom is replaced by sulfur. Form salts which are yellow hygroscopic powders with pleasant, aromatic odor. Chemical properties as similar to barbiturates. Pentothal is in this group.



**N-substituted barbiturates**. Made by condensing malonic acid with substituted ureas (methyl urea, ethyl urea, etc.) Form salts which are white powders chemically similar to barbiturates. Evipal is in this group.



**Chemical Properties**—Are white powders. Average melting point between 100° to 300°C. All are weak acids soluble in organic solvents and poorly soluble in water. Dissolve in bases to give salts; salts poorly soluble in organic solvents but soluble in water. Sodium salts most common; aqueous solutions of sodium salts are alkaline having between pH 8-10. Solutions of barbiturates unstable; hydrolyze on standing, or if boiled. Solutions for intravenous use prepared from drug in sealed, sterile ampules.



### TYPES OF BARBITURATES

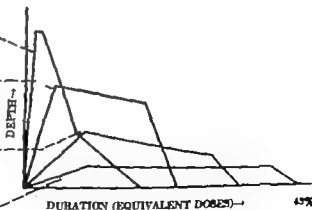
Over 1100 barbiturates are theoretically possible. Hundreds have been prepared. The clinically useful barbiturates, N-substituted barbiturates, and thio-barbiturates may be divided into four groups as follows:

**Ultra Short Acting**—Pronounced, intense hypnotic action, rapidly induced, of brief duration, followed by mild hypnosis or heavy sedation. Useful for abolition of consciousness during surgical procedures. Destroyed by liver. Most effective intravenously.

**Short Acting**—Moderate hypnotic action quickly induced (30 to 60 minutes) for four to eight hours followed by slight or no sedative effect (hangover). Useful for inducing sleep by oral use. Less commonly by intramuscular or intravenous injection. Rapidly detoxified by liver.

**Intermediate Acting**—Intense sedative action or mild hypnotic action. Onset gradual one to two hours lasting eight to twelve hours followed by slight sedative effect. Partly destroyed in liver. Used orally or intramuscularly.

**Long Acting**—Mild sedative action with little or no hypnotic effect in therapeutic doses. Onset and recovery gradual and action is sustained over many hours. Little or no destruction by liver in therapeutic doses. Eliminated in urine. Partly detoxified when massive doses are administered. Used orally or intramuscularly.



## BIOLOGICAL EFFECTS



**Surface Tension**—Surface tension of water lowered in vitro. Degree of lowering parallels narcotic potency. Possible similar effect on cell membrane postulated—causing narcosis. Rate and degree of hydrolysis in vitro does not parallel and is not related to narcotic efficacy.

**Absorption**—Readily adsorbed on activated surfaces such as ash-free charcoal; similar action may occur at cell membrane which decreases permeability and alters metabolism, which in turn causes narcosis.

**Lipid Solubility**—Lipid-water solubility ratios parallel narcotic potency. Behave like aliphatic compounds. Follow Overton-Meyer rule.

**Tissue Oxidation**—Reduced in vitro. Dehydrogenases inactivated. Oxidases not affected.

**Permeability of Cell**—Decreased. May cause metabolic changes which result in narcosis.

**Effects**—Barbiturates are central nervous system depressants. Possess no analgesic action. Cause psychic sedation, sleep, deep hypnosis or anesthesia. Effects vary with type drug, dose, mode of administration, rate of absorption, rate of destruction or elimination and susceptibility of the subject to drug.

## METHODS OF ADMINISTRATION AND USES

1. **Oral.** For sedation and hypnosis. Last four to eight hours or more. Rapidly absorbed from small intestine when administered orally. Slight absorption from stomach, unless massive doses are given.
2. **Rectal.** For sedation, sleep or basal hypnosis. Surgical anesthesia obtained with complementary inhalation anesthesia or regional block. Hypnosis lasts variable period of 4 hours more or less.
3. **Intraperitoneal.** For anesthesia in animals. Rapid and prolonged action of four or five hours duration.
4. **Intravenous.** One dose usually about 1 gram of an ultra-short acting drug administered rapidly in from 5% to 10% solution yields immediate deep hypnosis to complete anesthesia lasting for 30 to 90 second periods. Followed by sleep upon reacting. Cumulative action forbids repeating dose.

**Absorption**—Long, intermediates and short acting drugs are absorbed rapidly from small intestine when given by oral route and from large bowel by rectal route. Some absorption from stomach particularly when massive doses are given. Ultra short acting derivatives may be ineffective because they are rapidly destroyed unless injected directly into blood stream.

**Efficacy**—Measured by the minimum effective dose. In order of increase: barbital, phenobarbital, amytal, secobarbital, oral.

**Toxicity**—Measured by the minimum lethal dose. Does not parallel efficacy. In order of increase: barbital, secobarbital, dia, amytal, phenobarbital.

**Margin of Safety**—Ratio between the effective dose and toxic dose. In order of increase: phenobarbital, barbital, amytal, secobarbital, dia, secobarbital.

**Synergistic Action**—Efficacy of barbiturates increases if used in combination with analgesics such as pyramidal, salicylate, acetyl salicylic acid, codeine, amide, demerol, etc. Do not potential analgesic action of these drugs however.



The two hydrogens on carbon 5 may be substituted by aliphatic, aromatic or alicyclic radicals to yield compounds many of which possess hypnotic and sedative properties. Potency increases as molecular weight increases. When total number of carbons on both radicals begins to exceed 8 toxicity increases out of proportion to potency. Halogenation, unsaturation and branching of chain increase the potency, intensity and duration of action. Compounds possessing aliphatic radicals derived from secondary alcohols are more potent than those derived from primary.

Radical on Carbon 3	Radical on Carbon 5	Result
Short straight chain (ethyl)	Short straight chain (ethyl)	Long acting compound of low potency and toxicity (barbital)
Short straight chain (ethyl)	Long straight chain (butyl)	Increased potency, shortened duration, intermediate acting or short acting derivative (lurethal)
Short straight chain (ethyl)	Short branched chain (isopropyl)	Intermediate acting derivative (iprinal)
Short straight chain (ethyl)	Long branched chain radical derived from a primary alcohol (sec-amyl)	Intermediate to short acting derivative (amytal)
Short straight chain (ethyl)	Long aliphatic radical derived from secondary alcohol (sec-amethyl-butyl)	Short acting, high potency derivative (pentobarbital)
Short straight chain (ethyl)	Aromatic (phenyl)	Long acting, low potency derivative (phenobarbital)
Aromatic (phenyl)	Aromatic (phenyl)	No narcotic effect
Short unsaturated (allyl)	Short unsaturated (allyl)	Intermediate and short acting derivative of moderate intensity (dial)
Short straight chain with unsaturated linkage (vinyl)	Long straight chain	Short acting, high potency derivative (vinyl barbital)
Short unsaturated (allyl)	Long aliphatic derived from secondary alcohol (sec-amethyl-butyl)	Short acting, high potency derivative (secunal)
Short straight chain (ethyl)	Cyclic saturated	Short acting, high potency derivative
Short straight chain (methyl)	Unsaturated cyclic (cyclo-hexenyl)	Ultra short acting derivative of high potency (evipal)
Straight chain (butyl)	Unsaturated straight with halogens (bromo-allyl)	Short or ultra short acting derivative of high potency (permethon)

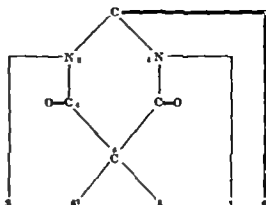
**DETOXIFICATION OR ELIMINATION**—Ultra short-acting and short-acting compounds are destroyed in the body probably in the liver. Destruction results in disruption of the malonyl urea ring. Degradation products may appear in the urine, particularly if large doses are administered. Intermediate-acting derivatives are partly destroyed in the body and partly excreted unchanged in urine.

Long-acting drugs are eliminated almost entirely unchanged in the urine. N-substituted derivatives (evipal) and the thiobarbiturates (pentothal) of higher molecular weight are not recovered in urine but are probably detoxified by the liver.

Halogenated unsaturated substituted barbiturates are eliminated with alterations in side chains with little breakdown of ring structure. Short acting drugs cause prolonged action when hepatic dysfunction is present, influenced little or none by renal insufficiency. Prolonged hypnosis results when long acting barbiturates are administered in presence of renal insufficiency but as a rule not affected by presence of hepatic insufficiency.

## PHARMACOLOGY OF BARBITURATES

Barbituric acid is a six-membered ring possessing the pyrimidine nucleus. The two hydrogen atoms on carbon 5 when substituted by aliphatic, cyclic, aromatic and other radicals yield numerous derivatives possessing hypnotic power. The hydrogen atoms on either nitrogen atom yield compounds called *N*-substituted barbiturates. The oxygen atoms on carbon 4 and 6 remain intact. Cyclic radical embodying carbon 5 results in spirobarbiturates.



Name	Fate	Action and Uses	5	5'	3	1	2
Barbital (U.S.P.) Medinal	Mostly unchanged, eliminated five to seven days in urine	Long-acting sedative	H	Ethyl	Ethyl	Na	O
Phenobarbital (U.S.P.) Luminal (proprietary)	Eliminated unchanged, recovered in urine	Long-acting sedative	H	Phenyl	Ethyl	N	O
Ipral (proprietary)	Partly destroyed and partly recovered in urine	Intermediate sedative	H	Ethyl	Isopropyl	Na Ca	O
Veronal (proprietary)	Partly destroyed and partly recovered in urine	Intermediate sedative	H	Ethyl	n-Butyl	H	O
Dial (proprietary)	Mostly destroyed, some in urine	Intermediate sedative	H	Allyl	Allyl	H	O
Alernia (proprietary)	Small part in urine, mostly destroyed	Intermediate hypnotic	H	Allyl	Isopropyl	Na	O
Sandepal (proprietary)	Destroyed, none in urine	Short-acting hypnotic	H	Allyl	Isobutyl	H	O
Ortal (proprietary)	Destroyed, none in urine	Short-acting hypnotic	H	Ethyl	n-Hexyl	Na	O
Amytal (proprietary)	Destroyed, less than 5% in urine	Short-acting hypnotic	H	Ethyl	Isamyl	Na	O
Freobarbital (U.S.P.) Ambetal (proprietary)	Destroyed, none in urine	Short-acting hypnotic	R	Ethyl	1-Methyl butyl	Na	O
Phenaceta (proprietary)	Destroyed, less than 5% in urine	Short-acting hypnotic	R	Ethyl	Cyclo hexenyl	H	O
Peronoxon (proprietary)	Destroyed, none in urine	Short-acting local hypnotic	R	$\beta$ -brom allyl	Butyl	H	O
Veronal (proprietary)	Destroyed, none in urine	Short-acting hypnotic	H	$\beta$ -brom allyl	Isopropyl	H	O
Erypal, Erypan Hexobarbitone	Destroyed, none in urine	Ultra short-acting local hypnotic	CH <sub>3</sub>	Methyl	Cyclo hexenyl	Na	O
Prothelal (proprietary) Thiopentone Thespenal	Destroyed, none in urine	Ultra short-acting local hypnotic	H	Ethyl	1-Methyl butyl	Na	S
Boronal (proprietary)	Destroyed, none in urine	Hypnotic	H	Allyl	1-Methyl butyl	Na	O
Veronal Verobarbital (proprietary)	Destroyed, none in urine	Hypnotic	H	Ethyl	1-Methyl 1-Butenyl	Na	O
Michael (proprietary)	Destroyed	Hypnotic anti-coagulant	CH <sub>3</sub>	Ethyl	Phenyl	N	O
Betonal (proprietary)	Partly destroyed	Sedative and mildly hypnotic	H	Ethyl	Sec. butyl	Na	O
Berital (proprietary)	Destroyed, none in urine	Rapid hypnotic	H	Methyl butyl	Allyl	Na	S
Thiothamyl (proprietary)	Destroyed, none in urine	Rapid hypnotic	H	Ethyl	Isamyl	Na	S
Aminal (proprietary)	Destroyed, none in urine	Rapid hypnotic	H	Allyl	Cyclo hexenyl	Na	S

A progressive depression of the central nervous system may be observed when many barbiturates are administered slowly intravenously. The phylogenetically newer portions of the cerebrospinal axis are affected first, giving rise to phenomenon akin to the planes and stages of narcosis observed in the case of aliphatic general anesthetics. Rapid administration of short and ultra short-acting barbiturates causes a telescoping and non-appearance of the following signs:

Stage	Site of Depression	Characteristics	Eye	Respiration	Circulation
I. Clouded consciousness	Cortex, slight to moderate depression.	Euphoria. Loss of discrimination to loss of appreciation of environment. Loss of coordination of motor activity.	Pupil size reaction to light and corneal reflex unchanged.	No significant change.	No significant change.
II. Hypersensitive	Cortex—complete depression. Subcortex—slight depression, particularly subthalamic and motor nuclei.	Motor activity and excitement absent. Increased sensitivity to external stimuli causes exaggerated movement.	Rolling eyeball. Corneal reflex becomes sluggish. Pupil size and reaction to light unaltered.	No significant change.	No significant change.
III. Basal Narcosis	a	Embryonic and diencephalic structures (thalamus, hypothalamus and basal ganglia depressed).	May oscillate or be fixed. Reaction to light disappears. Lid reflex depressed.	Mildly depressed.	Slight increase in pulse rate. Blood pressure changes slightly.
	b	Partial depression of mid-brain.	Pain carries changes in pupils and respiratory rate. Pupils remain constricted.	Usually fixed eyeball. Reaction to light gone. Corneal reflex depressed.	Increased pulse rate. Blood pressure may decrease.
	c	Complete depression of medulla and beginning to moderate depression of medulla.	Fixed. Reaction to light gone. Corneal reflex depressed.	Marked depression or apnea.	Increased pulse rate. Blood pressure may decrease.
IV. Medullary depression	Depression of medulla.	Depressed respiration. Circulatory collapse. Muscles relaxed.	Pupils dilate.	Apnea.	Blood pressure falls.

### TREATMENT OF MASSIVE OVERDOSAGE

**SYMPTOMS**—Coma, hypothermia early fever later sluggish or absent reflexes, respiratory depression and gradual appearance of circulatory collapse.

### TREATMENT

1. Institute adequate pulmonary ventilation—airway oxygen assisted or artificial respiration.
2. Remove stomach contents by aspiration or lavage (if orally ingested).
3. Support circulation if depression is present by administering fluids, blood etc.
4. Promote diuresis.
5. Lavage colon to remove drug excreted into large bowel.
6. Administer analeptic drug. Picrotoxin 1 mgm. per minute intravenously until patient begins to stir.
7. Administer antibiotics to prevent pulmonary complications.

## GENERAL REACTIONS OF LONG AND INTERMEDIATE ACTING BARBITURATES

**Cortex**—Spontaneous activity inhibited. Small doses cause sedation, large doses hypnosis. Sleep is dreamless and resembles natural sleep. Lower afferent pathways remain intact and transmit impulses to cortex. Pain stimuli arouse subject and induce delirium. Restlessness often follows recovery from deep hypnosis.

**Temperature Regulating Center**—No effect from sedative doses. Depressed by massive doses.

**Cough Center**—No effect. Massive doses depress.

**Feeding Center**—Depressed. Control centers in sedative doses.

**Vagus Center**—Cardiac portion of vagus depressed; respiratory portion remains active.

**Respiratory Center**—No effect by hypsotic and sedative doses. Depressed by large doses. Sensitivity to carbon dioxide decreased.

**Parasympathetic Center**—No significant effect in sedative and hypsotic doses. Directly depressed by massive doses. Blood pressure falls.

**Carotid-sinus Chemoreceptors**—No notable effect. Reflexly maintain respiration in overdosage. Depressed by massive doses.

**Lungs**—Alveolar volume exchange decreased due to psychic sedation. Respiratory rate may increase; amplitude decreases with large doses. Hering-Breuer reflex remains active. Massive doses cause central respiratory depression and respiratory paralysis.

**Metabolism**—No significant change in basal metabolic rate. Decreased by massive doses. Reduction in hyperthyroidism due to sedative effect.

**Liver**—Hypsotic doses have no effect. Massive doses decrease function (dyk test). Glycogen content decreased by massive doses.

**Kidney**—Hypsotic doses have no effect on renal function. Oliguria followed by polyuria from decreased water diuresis in deep hypnosis. Probably due to action on hypothalamic pituitary system. Urinary output returns to normal within 8 to 24 hours after recovery.

**Splanchnic**—Unaffected by sedative and hypsotic doses. Relaxed with massive doses.

**Reflexes**—Mild depression of superficial reflexes. Deep reflexes exaggerated in hypnosis. All are depressed in deep hypnosis.

**Striatal Muscles**—Tense when given with sedative doses; relaxed in deep hypnosis from massive doses. Contractions controlled by intravascular doses by action on cortex (paleocortical) subcortical structures and cord. Glycogen content unchanged.

**Skin**—Temperature increases from peripheral vasodilatation. Rash due to sensitivity or prolonged use of some drugs not uncommon.

**Hypothalamus**—Depressed thought to be primary site of action.

**Cerebral Vessels**—Sedative and hypsotic doses cause no change. Dilated by large doses.

**Intracranial Pressure**—Unchanged. Decreased by massive doses, probably secondary to hypotension. Spinal fluid concentration insignificant.

**Eyes**—Pupils remain in mid-dilatation. Movements of eyeballs remain active with sedative doses. Fixation with massive doses. Corneal reflex remains active. Depressed by massive doses. Constricted pupils often seen with overdosage.

**Mucous Membranes**—Ciliary activity not affected. Depressed by massive doses.

**Salivary Glands**—Little effect during sedation or hypnosis. Secretions depressed by massive doses.

**Pharynx**—No effect on gag reflex. Reflex absent only in deep hypnosis. Tongue may relax and cause obstruction in deep hypnosis.

**Larynx**—Laryngeal reflex remains active. May be exaggerated during hypnosis. Stimulation may cause spasm. Absent in very deep hypnosis.

**Heart**—No notable effect on myocardium. Depressed by massive doses. Not unchanged during hypnosis or sedation. Tachycardia with massive doses. No notable effect on rhythm. Arrhythmias of various types with massive doses.

**Blood Pressure**—No significant effect in hypsotic doses. Massive doses cause hypotension due to depression of vasomotor centers and heart. Increased capillary permeability from massive doses.

**Spleen**—No effect in sedative or hypsotic doses. Dilated in deep hypnosis. Red cell content increases.

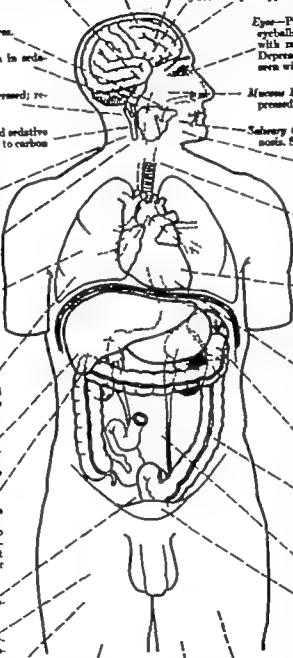
**Gastrointestinal System**—Sedative and hypsotic doses cause an antiperistaltic action due to central depression and removal of psychic influences. Large doses depress smooth muscle and decrease motility.

**Pancreas**—Secretions unaffected. Blood supply less unchanged.

**Uterus**—No effect from sedative and hypsotic doses. Contractions and tone decreased by massive doses. Pass through placenta to fetus causing respiratory depression. Fetal arterial oxygen content unchanged ordinarily.

**Body Temperature**—Unchanged by sedative and hypsotic doses. Decreased by massive and toxic doses due to reduced metabolism, vasodilatation and depressed activity of heat regulating center.

**Habituations**—Frequent. Tolerance (psychological dependence) and cross tolerance common. Addiction (physical dependence) unusual. Withdrawal symptoms unusual. Overdosage from automatic frequent in self medication.



**Red Blood Cells**—Decrease in number. Increase in cell volume frequent.

**Glucose**—No significant changes with sedative and hypnotic doses. Elevation with doses which cause deep hypnosis or basal narcosis.

**White Cells**—No significant changes. Increase after deep hypnosis.

**Bleeding Time**—Unchanged.

**Oxygen Capacity**—Not significantly altered. Usually decreased.

**Clotting Time**—Unchanged.

**Carbon Dioxide Content**—No change or slight elevation. Increased with massive doses.

**Inorganic Ions**—No significant changes.

**Carbon Dioxide Combining Power**—Variable. Slight or no change with sedative and hypnotic doses. Massive doses cause lowering of pH due to accumulation of fixed acids.

**Non-protein Nitrogen**—No significant changes unless oliguria follows, which causes elevation.

## URINE

**Output**—Decreases during hypnosis and returns to normal within 24 hours.

**Water Diuresis**—Decreased with return to pre-hypnotic values after deep hypnosis or in toxic doses. Long and intermediate acting drugs in therapeutic doses are recovered in urine short and ultra short-acting only after massive doses.

## PATHOLOGY

No significant or characteristic histological changes ascribable to the drug.

## USES

- (1) For hypnosis.
- (2) To antagonize convulsions from stimulating drugs.
- (3) As basal or pre-anesthetic sedation.
- (4) In psychiatric interviews.

## ADVANTAGES OVER OTHER HYPNOTICS

- (1) Causes few side effects or metabolic disturbances.
- (2) No effects on blood-forming organs.
- (3) Tolerance develops slowly.
- (4) Cumulative effects occur slowly.
- (5) Sleep resembles natural sleep.
- (6) Physical dependence uncommon.

## DISADVANTAGES

- (1) Large doses cause severe respiratory depression.
- (2) Non-analgesic.

## CONTRAINDICATIONS

- (1) Hepatic diseases.
- (2) Shock-like states.
- (3) For analgesia.

## ULTRA SHORT ACTING BARBITURATES (THIOPENTAL)

**SYNONYMS**—Pentothal, thioembutal, thiopentobarbital, thiopentone 8064 thiobarbiturate A.

**HISTORY**—First attempt at intravenous injection in man was by Christopher Wren (London, 1637) First attempt at intravenous anesthesia by Sigismund Elsholtz in 1665 using an opiate solution. Ore of Lyons, France (1862) produced anesthesia in man using intravenous chloral hydrate. Krawk in 1905 produced anesthesia with intravenous Medonal Burkhardt (Germany 1909) described intravenous use of narcotics, ether and chloroform. Noel and Soutter (1913) described intravenous use of paraldehyde. Then followed use of magnesium sulphate (Peka Nellser) alcohol (Naka gawa 1921) Avertin (Kirshner 1929) somnifen (barbiturate) (Germany 1924) pernoston (1927) Amytal (Lundy 1929) Nembutal (Waters 1929)

First successful use of ultra short-acting barbiturate was in Germany by using Evipal (Weese 1933) Thiopental first used experimentally by Tatum, Waters and co-workers and clinically by Lundy and Torrell (1934) at the Mayo Clinic.

**SYNTHESIS**—Diethyl malonate is treated with ethyl bromide in the presence of sodium ethoxide, and converted to diethyl malonate. This is then alkylated with 2 bromo-pentane which results in 1,5 diethyl methyl butyl ethyl malonate. This is then condensed with thioacetone in the presence of sodium ethoxide which results in 5 ethyl 5 methyl butyl thiobarbituric acid. The pure acid is precipitated from an aqueous solution of the reaction mixture by the addition of an acid.

**PROPERTIES**—Thiopental is a pale yellow hygroscopic powder with a bitter taste which is readily soluble in water and partly soluble in alcohol insoluble in ether and benzene. Oil/water partition coefficient is 4.7 (0.814 pentobarbital). Six parts of sodium carbonate are added per 100 parts to prevent precipitation of insoluble free acid by atmospheric carbon dioxide and to serve as a buffer. Aqueous solutions are strongly alkaline pH of 2% solution equals 10.5-11.

**STABILITY**—Atmospheric carbon dioxide precipitates the free acid from aqueous solutions. Solution not boilable or stable on standing. Packed in sealed ampules to prevent deterioration. Powder stable for several years. 5% solution deteriorates on standing at room temperature. Unclear solutions not fit for clinical use. At 20°C particles appear in solution on third day. At 5° cloudiness delayed until the eighth day.

Not compatible with acidic substances. Compatible with blood, saline and dextrose solutions.

**Effect**—Acts primarily at this site. Depresses from here downward. Amount of depression varies with dose and rapidity of administration. Additional fractions depress subcortical areas of brain stem. Easily penetrates blood brain barrier. Onset of hypnosis abrupt within 30-40 seconds. Recovery rapid after small dose with some somnolence and retrograde amnesia. Not an analgesic. Presumably does not block mesencephalic system. Blocks reticular activating system. Must be combined with narcotic or anesthetic (N<sub>2</sub>O) to block reflex activity. Induces convulsions, particularly those of cortical origin. Less effective for those of spinal or other origin.

**Electroencephalogram**—Free definitely reproducible levels are recognized.

**Level I**—High amplitude fast wave, spiky in appearance. Interspersed with fast waves of slightly low amplitude—75-80 microvolts, 10-20 cycles per sec.

**Level II**—Flow wave forms irregular continue that form of random. Wide variation in frequency. Two cycles per sec or more in amplitudes up to 150 microvolts. "Spiky" waves of irregular amplitude at frequencies of 10 cycles per sec are superimposed on and between slow wave patterns.

**Level III**—Suppression appears. Discharge bursts within intervening quiet period. Suppression less than 2 sec duration. First phase has frequency of 10 cycles per sec. Second phase 2 or more slow wave, 2 cycles per sec merging into the next suppression.

**Level IV**—Suppression phases lasting 5-10 sec appear. Activity as in Level III with low amplitude.

**Level V**—Amplitude decreased to less than 25 microvolts and single wave appear at 10 or more sec intervals.

**Brain**—No localization of barbiturates in any subdivision of the brain. A lag in uptake by the brain. Peak is attained by thiobarbiturates in 7 minutes. Brain exerts less destructive action than other tissues and retains drug longer. Possibly due to binding by protein. 5% or more thiopental bound to protein of brain.

**Intracranial Pressure**—Unchanged ordinarily. May be decreased if hyperventilation develops. May increase in hyperventilation. Concentration of drug in plasma and spinal fluid parallel each other. May cause apnea if administered when pressure is increased. Spinal fluid varies with amount of CO<sub>2</sub> retained.

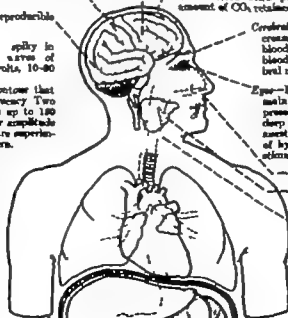
**Cerebral Blood Flow**—Blood flow increased due to increased tone of cerebral vessels due to increased blood CO<sub>2</sub> from respiratory depression. Cerebral blood flow varies with amount of CO<sub>2</sub> retained. Cerebral metabolism reduced.

**Eyes**—Pupils react to light during light hypnosis. Remain contracted. Nystagmus or divergent strabismus present. Eyeballs fixed. Pupils in mid-dilation in deep hypnosis. Pupils become normal in time in light anesthesia. Eye signs not satisfactory index of depth of hypnosis. Corneal reflex remains active. Corneal stimulation during eye surgery affects sneezing.

**Gills**—Activity reduced.

**Salivary Glands**—No production or secretion of mucus. No irritation to the mucous membranes. Secretions cease to form during narcosis.

**Thyroid**—No effect. Patients with hypothyroidism manifest intolerance. If perthyroids may manifest increased tolerance.



**Temperature Regulating Center**—Depressed. Body temperature falls. Hypothermia develops when placed in cold environment. Shivering occurs on recovery if exposed to a cold environment. Body temperature falls.

**Respiratory Center**—Depressed. Becomes progressively less sensitive to carbon dioxide.

**Vagus Center**—Remains active.

**Pressor Center**—Depressed during induction and during narcosis. Blood pressure may fall during induction but returns to normal during maintenance. May be depressed before respiratory center.

**Vomiting Center**—No stimulating effect on center proper or chemoreceptor zone. May depress center and inhibit vomiting. Post-anesthetic vomiting due to drug itself uncommon. Post-surgical vomiting due to factors other than anesthesia occur.

**Cerebral Aortic Chemoreceptors**—Depressed by large doses. Remains active ordinarily and reflexly stimulates respiration when respiratory center sensitive to carbon dioxide and hyperventilation causes apnea. Administration of oxygen causes apnea by removal of chemoreceptor drive.

**Lungs**—Potent respiratory depressant. Rhythm may be irregular. Rate and depth of breathing are decreased. Minute volume exchange reduced. Apnea common after initial injection. Total blood  $\text{CO}_2$  increased. Carbon dioxide tension increased (alveolar).

**Bronchi**—Bronchi constricted. Bronchial spasm easily initiated by endoscopic instruments, secretions or foreign bodies. More common in asthmatics and bronchial-pulmonary diseases. Bronchospasm activity due to selective increase in reflex by thiobarbiturates. Prevented by blockade of larynxes with topical anesthetics. Atropine decreases reflex activity and secretions which act as stimulants.

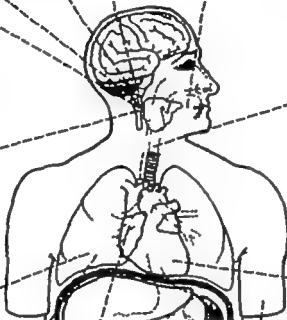
**Pharynx**—Pharyngeal or gag reflex not abolished. May be accentuated. Local stimulation by larynx, laryngoscope, secretions may elicit cough, retching or severe laryngeal and bronchial spasm. Topical anesthesia blocks afferent impulses and prevents spasm.

**Larynx**—Laryngeal reflex not abolished. May be accentuated and be hyperactive. Severe laryngeal spasm may develop after instrumentation or stimulation by laryngoscopy, blood, mucus, or other stimuli. Topical anesthesia blocks afferent impulses and prevents spasm. Atropine and morphine except in bolus secretions which may stimulate. Severe spasm associated with neurolept analgesia (striated muscle) blocking agents. Spasm frequent when used as induction agent for "irritating" anesthetics, such as ether.

**Heart**—Direct myocardial depressant. Degree of depression proportional to the amount of drug in contact with the heart. Repeated injections have cumulative effect on the heart. Unhealthy myocardium more susceptible to drug than healthy.

Arrhythmias may appear due to retention of  $\text{CO}_2$ . Unconscious with adequate ventilation, P-R interval may be shortened. Does not sensitize the heart to epinephrine or other sympathomimetic amines. Rapid administration may cause severe myocardial depression and cardiac arrest. Rate variable, usually increased to compensate for vascular dilatation and other vascular changes.

**Blood Pressure**—Effects vary with the rate of injection, state of the heart, peripheral circulation and quantity used. Rapid, intravenous injection causes abrupt fall in blood pressure accompanied by apnea. Slow injection may cause elevation at onset with widening of pulse pressure due to  $\text{CO}_2$  retention (vasodilation) and depression of vasomotor center. Reduction in pressure in hypertensive.



**Metabolism**—Reduced during hypnosis; oxygen consumption decreased. Detention clearly when metabolism is decreased causing prolonged hypnosis.

**Dysphagia**—Hiccups may occur from manipulations of upper abdomen or when phrenic nerve is stimulated during operation.

**Liver**—Function not significantly altered. Liver glycogen depleted after large doses. Icteric index not changed. Hepatic dysfunction prolongs hypnosis effect. Bulk of drug detoxified here.

**Adrenal**—Adrenalectomy prolongs time required for detoxification.

**Kidney**—No evidence of damage to normal kidney. Less than 0.5% excreted unchanged in urine. Urinary output not markedly affected by ordinary anesthetic doses. Toxic doses cause temporary anuria. Renal vasoconstriction in deep hypnosis reduces renal blood flow and glomerular filtration. Causes oliguria.

**Respiratory**—Not relaxed ordinarily. Attempts at dilatation may initiate severe bronchospasm or bronchial spasm.

**Spinal Cord**—N effect on cord reflexes. Reflex responses to stimuli not abolished. Produces spinal block if injected intrathecally. Highly irritating to nerve tissues. Causes irreversible changes in cord.

**Brain Nerves**—No suppression of activity. May be injected into subarachnoid cavity in absence of value.

**Nerve**—Produces blockade when applied perineurally. Irritating to peripheral tissues.

**Reflexes**—Deep reflexes depressed in deep basal narcosis. Reflexes active in ordinary hypnosis doses. Superficial reflexes may be present in light hypnosis but depressed in deep hypnosis. Painful stimuli cause movement due to failure to block pathways from periphery to cortex. Movements due to lack of analgesic activity. Anesthesia develops with loss of all reflexes in massive doses, presumably due to block of lumbar-thalamic system.

**Rectal**—Absorbed by the rectum. Produces local anesthetic not adequate for surgical anesthesia. Doses need 1 gram per 80 lb. body weight. Usually administered as 10% solution, 0.5 cc per lb. of body weight. Maximum dose should not exceed 3 grams.

**Local Irritation**—Highly irritant to subcutaneous tissues and fatness of arteries due to high alkalinity. Necrosis or thrombosis occurs in tissues if extravasation occurs. Inadvertent injection into radial artery causes severe spasm which may be followed by gangrene. Spasm frequent with more concentrated solutions. Treatment: Use vasodilating block and anticoagulant. Venous thrombosis occurs in small percentage of cases.

**Effect of Nucleic Acids**—No alteration on plasma levels, plasma theore, electroencephalogram or sleeping time.

**Autonomic Nervous System**—Effects variable. No apparent change may be present in some cases. Generally parasympathetic effects appear to predominate. Heart more responsive to vagal impulses. Bronchial constrictor tone increased.

**Gastro-intestinal System**—Effects variable. Smooth muscle depressed by large doses. Light hypnosis causes general increase in tone. Drug destroyed on passage through gastro-intestinal tract. Thiobarbiturates ineffective if administered orally except in large doses.

**Spleen**—Usually constricted if blood pressure rises or hypoventilation is present. May dilate.

**Uterus**—Frequency and amplitude of contractions remains unchanged in light hypnosis, reduced in deep hypnosis. Drug passes through placental membranes to the fetus and causes respiratory distress at birth. Fetal arterial blood content equals maternal blood content after 15 minutes.

**Muscle**—Ordinarily muscle relaxation inadequate for surgery. Necessitates use of muscle relaxants. Relaxed in deep hypnosis and in toxic doses. External stimuli during light hypnosis increase muscle tone. Exerts little or no curariform effect. Causes irritation when injected into muscle but not as pronounced as succinylcholine.

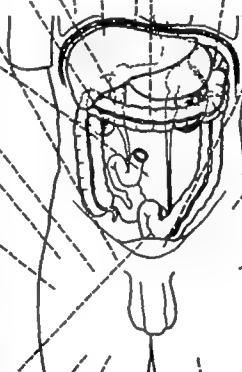
**Skin**—Temperature rises several degrees due to peripheral vasoconstriction. Sweating absent. Skin remains dry and pink. Skin rashes due to allergy possible but rare.

**Tissue Concentrations**—Plasma concentration falls rapidly for the first 15 to 30 minutes after single intravenous injection. Maximum tissue concentration reached one minute after injection, thereafter declines at a rate parallel to plasma level in all tissues except muscle and fat. Muscle concentration attains equilibrium within 15 minutes after injection. Initial short action due to diffusion from brain to blood and to rapid uptake by tissues. Equilibrium attained by plasma brain and body tissues as successive doses are added. Rate of destruction slow—10–15% per hour.

Stored in adipose tissues. Perirenal omentum and lumbar fat contain 3 to 12 times plasma level. Muscle only 1–3 times. Lipids contain 80 times as much as muscle. Peak level in adipose tissues occurs within 2 hours, not complete until 4 hours later.

Metabolized completely in man. 25% oxidized to carboxylic acid. Less than 8% desalicylated. Cumulative effect observed if dose is repeated within 80 hours. Carboxyl group is on terminal carbon of methyl butyl side chain.

**Tolerance**—Acute tolerance develops to rapid injection. Chronic tolerance to repeated injection. Second injection after several days produces less effect than first. Cross tolerance also seen with other barbiturates.





**Oxygen Capacity**—Usually unchanged if ventilation is adequate.

**Oxygen Content**—Venous and arterial content not significantly changed.

**Blood Sugar**—Variable, slightly increased or unchanged in both normal and diabetic patients.

**Clotting Time**—Unchanged.

**Bleeding Time**—Unchanged.

**Van-protein Nitrogen**—No significant changes.

**Red Blood Cells**—No significant hemolysis due to intravenous injection. No hematuria. No intravascular hemolysis. No changes in morphology.

**Blood Concentration**—Plasma level falls rapidly after injection. Acidosis suppresses blood level. Concentration of drug at which the patient awakes increases as duration proceeds. Patient awakes at higher plasma level when large initial dose has been used than after small dose. Acute tolerance develops to narcotic effect. Equilibrium develops between tissues, brain and plasma after successive fractional administration.

**Blood Volume**—Usually no change. Slight hemodilution may occur. Hemocoagulation may occur with hypoventilation.

**Plasma Volume**—Usually no change. May increase slightly.

**Red Blood Cells**—Usually no change. Usually increased in number with hemocoagulation and decreased if hemodilution is present.

**Carbon Dioxide Content**—Increased due to depression of respiration. Causes respiratory acidosis. Increase proportional to depression.

**Carbon Dioxide Combining Power**—No significant changes in light hypnosis. May decrease in deep hypnosis.

**Blood pH**—Usually slightly decreased due to respiratory acidosis. Decrease of pH suppresses plasma level due to the formation of the free acid which passes into the fat. Decrease of pH from 7.35 to 6.8 (with  $\text{CO}_2$ ) reduces plasma level 60%.

**Blood Protein**—No significant changes. Barbiturates bound to protein—mainly albumin. Degree of binding varies with pH. Binding is reversible and dependent upon albumin concentration. As much as 90-70% (thiopental) adsorbed to protein. Binding maximal at pH 8. Bound compound does not play role in hypnosis.

## USES

1. As an anesthetic for brief surgical procedures.
2. As a basal hypnotic to supplement nitrous oxide, ethylene and other anesthetics of low potency or in combination with analgesics.
3. To relieve convulsive states produced by stimulating drugs or other causes.
4. As a hypnotic in conjunction with regional anesthesia (spinal, nerve block, etc.).
5. For pre-analgesia in psychiatric disorders and neuro-interrogation in criminal investigation.

## MODE OF ADMINISTRATION

Intravenous. In fractions using 1-2% solution. Total dose not to exceed one gram. Not suitable as a sole agent. Should always be employed with an agent with analgesic properties to abolish reflex activity and minimize total quantity used. Test dose of 30 mgm. to detect tolerance advised.

## ADVANTAGES

1. Induction simple, rapid, pleasant.
2. Requires a minimum of apparatus.
3. Non-irritating to the respiratory tract.
4. Does not cause formation of acroleins.
5. Allows the use of entropy and other devices which may be source of ignition.
6. Recovery rapid without nausea and vomiting after minimal doses.

## DISADVANTAGES

1. Not analgesic. Requires use of nitrous oxide, vinyl ether trichloroethylene, xenon, or other analgesic agents.
2. Causes severe respiratory depression.
3. Non-controllable as a sole anesthetic.
4. Convulsive action invariably occurs if one gram doses are exceeded.
5. Muscle relaxation not adequate (see relaxant).
6. Superficial reflexes not abolished. Painful stomach cramp movement.
7. Sometimes irritating—may produce slough, thrombosis or arterial spasm.
8. Variations in susceptibility between patients.
9. May be proconvulsant.
10. Prolonged somnolence may develop in tolerant individuals or those with depressed metabolism.

## PATHOLOGY

No pathologic effects directly ascribable to the drug noted in acute toxicity. No specific lesions in chronic toxicity. Neurologic changes in brain may follow acute poisoning with massive overdoses in recovery period, probably due to anoxia.

## CONTRAINDICATIONS

1. Ambulatory patients.
2. Intoxication already before induction—obesity Ludwig Anger, compression of trachea, etc.
3. Porphyria.
4. Respiratory distress—status asthmaticus, dyspnea, orthopnea, etc.
5. Acidosis from any cause, renal, diabetic or other.
6. Addison Disease.
7. Cardiac decompensation.
8. Shock.
9. Situations which may prolong narcotic effect—over-pramedication, hepatic dysfunction, acidosis, etc.
10. Situations in which airway cannot be maintained after induction.
11. Severe ocular hypotension.
12. Elevated intracranial pressure.
13. Severe hypothyroidism.
14. Dismatocrosis.

## USE UNDESIRABLE

1. Children.
2. Myasthenia gravis.
3. Obstetrics.
4. Myocardial diseases with poor reserve.
5. Barbiturate reduced pulmonary reserve.

## ULTRA SHORT ACTING THIOBARBITURATES

Name	Thiobarbital	Mebarbital	Thiohexethal	Butalbital
Synonyms	Seroral	Servoral, Thiopental	Kemithal	Tranthal, Rytal
History	Developed by Parke, Davis Laboratory	Introduced by Meiselman 1951.	Carington (England 1950)	Used clinically by Pines & Koss 1944.
Chemical Name	3-allyl 5'-methyl butyl thiobarbiturate sodium.	3-butyl 5'-methyl (3-methyl barbiturate sodium.	3-allyl 5'-cyclohexenyl thiobarbiturate sodium.	3-allyl 5'-isobutyl thiobarbiturate sodium.
Oral presentation	Suspension	None	None	None
Color	Pale yellow powder	Pale yellow powder	Pale yellow powder	Pale yellow powder
pH of 5% salt solution	Unstable solution 10.5-11	Unstable solution 10.5-11	Unstable solution 10.5-11	Unstable solution 10.5-11
Palatability	Similar to thiopental.	Half of thiopental.	Similar to thiopental.	Similar to thiopental.
Administration	Similar to thiopental. 2% I.V.	As 5% or 10% solution.	As 5-10% I.V.	As 10% solution I.V.
Maximum Dose	Slightly less than thiopental.	Greater than thiopental. Not to exceed 8 gram.	Half as potent as thiopental.	1-1.5 grams.
Anesthetic Dose	Slightly less than thiopental.	Greater than thiopental.	Equivalent doses produce same effect.	0.5-0.5 gram.
Onset of induction	Similar to thiopental.	Rapid but not "smooth."	Rapid but not "smooth."	Rapid but not "smooth."
Recovery	More rapid than thiopental.	More rapid than thiopental (1 time)	More rapid than thiopental.	More rapid than thiopental (1 time)
Postoperative effects	Fewest. Similar to thiopental.	Fewest. Less than thiopental.	Fewest. Less than thiopental.	Fewest. Less than thiopental.
Laryngeal Irritation	Fewest as thiopental. Causes cough, laryngismus, arterial spasm.	Fewest as thiopental. Causes cough, laryngismus, arterial spasm.	Fewest as thiopental. Causes cough, laryngismus, arterial spasm.	Fewest as thiopental. Causes cough, laryngismus, arterial spasm.
Reflexes	Similar to thiopental. Palatal reflexes cause emesis.	Similar to thiopental. Palatal reflexes cause emesis.	Similar to thiopental. Palatal reflexes cause emesis.	Similar to thiopental. Palatal reflexes cause emesis.
Cerebral metabolism	Similar to thiopental.	Similar to thiopental.	Similar to thiopental.	Similar to thiopental.
Cerebral blood flow	Similar to thiopental.	Similar to thiopental.	Similar to thiopental.	Similar to thiopental.
Electroencephalographic changes	Fewest as thiopental.	Fewest as thiopental.	Fewest as thiopental.	Fewest as thiopental.
Cerebral effects	Twifolding above. Inhibits cerebral motor cortex as thiopental.	Twifolding above. Inhibits cerebral motor cortex as thiopental.	Twifolding above. Inhibits cerebral motor cortex as thiopental.	Twifolding above. Inhibits cerebral motor cortex as thiopental.
Myocardial effects	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.
Cardiac Rhythm	Arrhythmias absent.	Arrhythmias absent.	Arrhythmias present.	Arrhythmias absent.
Pulse Rate	Increases in pulse rate.	Slight increase, less than thiopental.	Slight increase in pulse rate.	Slight increase in pulse rate.
Blood Pressure	Post-injection depression	Post-injection depression 10-25% for arterial anastomosis. 45 partial recovery	Decrease post-injection 10-25% with partial recovery	Post injection decrease with partial recovery
Respiration	Depresses. Qualitatively similar to thiopental.	Depresses. Qualitatively similar to thiopental.	Depresses. Qualitatively similar to thiopental.	Depresses. Qualitatively similar to thiopental.
Laryngeal and bronchospasm	Spasmodic, similar to thiopental	Greater frequency than thiopental.	Similar to thiopental.	Spasmodic, coughing, sneezing, laryngism.
Body temperature	Depresses motor similar to thiopental	Depresses motor similar to thiopental.	Depresses motor similar to thiopental.	Depresses motor similar to thiopental.
Blood brack barrier	Fewest penetration. Rapid onset. Equal to thiopental in uptake.	Early penetration. Rapid onset. Equal to thiopental.	Early penetration. Rapid onset. Equal to thiopental.	Early penetration. Rapid onset.
Uptake by adipose tissues	11 times greater than thiopental. Accounts for rapid recovery.	Rapid, equal to thiopental. Accounts for rapid recovery.	Similar to thiopental but 5% less. Accounts for rapid recovery.	Similar to thiopental. Accounts for rapid recovery.
Effects on smooth muscle	Depresses in deep hypnosis	Depresses in deep hypnosis.	Depresses in deep hypnosis.	Depresses in deep hypnosis.
Effects on uterus	Fewest placental barrier. Depresses fetal respiration	Fewest placental barrier. Depresses fetal respiration	Fewest placental barrier. Depresses fetal respiration.	Fewest placental barrier. Depresses fetal respiration.
Elimination	In liver similar to thiopental.	In liver 50% per hour	Metabolized by liver 5.5% eliminated unchanged.	In liver similar to thiopental.
Effects on muscle relaxants	Qualitatively similar to thiopental	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.
Neurolept analgesia	Not adequate. Relaxant required.	Not adequate. Relaxant required.	Not adequate. Relaxant required.	Not adequate. Relaxant required.

## N-SUBSTITUTED BARBITURATES AND SHORT ACTING BASAL NARCOTICS

Name	Thiobarbitals	Methobarbitals	Barbitone	Gluethimide
Synonym	Ecogen, ecogen, barbituricum	Brevital	M.B.P. 133	Davidon
History	Wass (Germany) 1928	Developed by Gruber 1933	Introduced by Landy 1965	Prepared by Tappan, et al. 1928
Chemical Name	<i>N</i> -methyl- <i>N</i> -cyclohexenyl- <i>N</i> -methyl barbituric acid	<i>N</i> -allyl- <i>N</i> -methyl- <i>N</i> -propyl- <i>N</i> -methyl barbituric acid	<i>N</i> -ethyl- <i>N</i> -phenyl barbituric acid	Alpha ethyl phenyl glutamide
Oxygen analogue	None	None	None	None
Color	White, stable	White, stable	White hygroscopic powder	White
pH of <i>N</i> salt solution	Usable pH 5-10	Usable pH 5-10	Acid insoluble $\frac{1}{2}$ N salt soluble 11.5-12.0 crystalline out on standing	Insoluble in water soluble in aqueous solutions
Potency	Non-analgesic, compares with thiopental	Non-analgesic, more potent than thiopental	Non-analgesic, less potent than thiopental	Non-analgesic, less potent than thiopental
Administration	10% solution I.V. rapid	10% solution by drip technique	Intravenously as 0.5% solution	Only satisfactory orally as tablet for hypnosis I.V. in propofol given
Maximum Dose	1 gram	0.5-0.8 gm.	1 gram	0.25-0.5 gm orally
Anesthetic Dose	0.1-0.8 gm.	0.0-0.8 gm. I.V.	0.0-0.8 gm.	Absent 1 gm potent as thiopental
Onset of action	Not as smooth as thiopental	Smooth without excitement	Rapid onset, smooth	Not satisfactory intravenously
Recovery	More rapid than thiopental	More rapid than thiopental	Rapid 10% concentration	One day hypnosis is obtained if it is sustained for hours
Longer effects	Present, for several hours observed	Present, for several hours observed	Present, but not as intense as with thiopental	Present
Local Irritation	Less than with thiopental	Less than with thiopental	Marked local irritation	Paravertebral solution causes phlebitis
Reflexes	Not abolished, Pupil's stomach some movement. Not analgesic	Not abolished, Pupil's stomach some movement. Not analgesic	Not abolished, Pupil's stomach some movement. Not analgesic	Mildly depresses. Not analgesic
Central metabolism	Depressed	Probably depressed		Depressed
Coronary blood flow	Decreased			
Fluorescence-graphic changes	Decreased activity similar to thiopental	Similar to thiopental—4 cycles per sec.	Decreased activity	Same as thiopental
Correlative effects	Twice as potent as thiopental	Twice as potent as thiopental	Absent Anesthetics curve, same	Absent
Myocardial effects	Similar to thiopental	Similar to thiopental	Depresses, qualitatively similar to thiopental	Subsides dose no effect
Cardiac rhythm	No irregularities	Absent	Absent	No effect in sublethal doses
Pulse Rate	Increased	Increased	Increased	Not altered in sublethal doses
Blood Pressure	Post injection depression	Post-injection depression	Post injection depression	Slight hypotension I.V.
Respiration	Depressed, less than thiopental	Depresses, similar to thiopental	Depressed, less than thiopental	No effect in hypolethal doses
Laryngeal and bronchial reflexes	Active, less than thiopental	Active, less than thiopental	Active, laryngeal and bronchial reflexes obtained	Active, Large doses obtained
Body Temperature	Depressed	Depressed	Depressed	Depressed in overdose
Blood Brain Barrier	Rapid penetration, equal to thiopental	Rapid penetration, equal to thiopental	Rapid penetration, equal to thiopental	
Uptake by Adipose Tissue	Uptake approx. 1/2 that of thiopental	Less than thiopental	Equal to thiopental	Taken up by lipids
Effects on Smooth Muscle	Depresses	Depresses	Depresses	No appreciable effect in hypolethal doses
Effects on Uterus	Similar to thiopental. Pains into fetal circulation	Similar to thiopental. Pains into fetal circulation	Pains placental barrier	Pains placental barrier
Destruction	Detected by destruction in liver	Rapidly destroyed by liver	Similar to thiopental	Excreted in bile and re-absorbed
Effects with Muscle Relaxants	Similar to thiopental	Compatible. Similar to thiopental	Similar to thiopental	Not used
Muscle Relaxation	Poor. Faccurates prevent through-out	Poor. Faccurates and other signs of neuromuscular activity	Poor. Tremors and fasciculations absent	Poor. Tremors and fasciculations absent

## URETHANES (CARBAMATES) AND SUBSTITUTED UREAS

	Urethane	Hedonal	Aponal	Carbominal	Bromominal	Bardominal
History		Used as an intravenous anesthetic by Page in 1912.		Introduced by Bayer. Also known as uredal, adalax.	Bromominal.	Developed by Roche Laboratory.
Chemistry	Ethyl ester of carbamic acid. Colorless, odorless crystals—very soluble in water, alcohol.	Carbamic acid ester of methyl propyl carbamate. White powder melts at 76 to 76°. Soluble in water and organic solvents.	Tertiary amyl carbamate. White crystalline powder with a camphorlike odor. Soluble in water and organic solvents.	White crystalline odorless powder. Slightly soluble in water. Soluble in organic solvents. Melts at 116 to 117°C.	Monobromoisovaleryl urea. White tasteless powder. Melts 147 to 148°. Soluble in cold water and organic solvents.	Allyl isopropyl acetylcarbamate. White t t t as powder melting at 191. Insoluble in cold water. Similar to carbominal. Soluble in hot and organic solvents.
Potency	Mildly hypnotic. More potent in animals than man. Rapidly absorbed from the G.I. tract. Not analgesic. Hypnosis lasts four or five hours.	Twice as potent as ethyl urethane. Esters of secondary alcohols are more potent than primary. Not analgesic.	Somewhat more potent than hedonal. Esters of tertiary alcohol are more potent than secondary. Not analgesic.	Freely hypnotic with potency similar to bromides. Not analgesic.	Similar to carbominal in potency. Possesses no analgesic properties.	Similar to carbominal.
Toxicity	May arrest cell mitosis. Depresses bone marrow. Excreted as urea after hydrolysis. Probably by detoxified liver.	More toxic than urethane. Absorbed more slowly. Believed to be excreted as urea and amyl alcohol after hydrolysis.	Similar to hedonal. Excreted as urea and amyl alcohol.	Eliminated partly unchanged in urine and partly in form of inorganic bromide.	Similar to carbominal.	Similar to other substituted amides. Causes depression of platelet production, resulting in thrombocytopenic purpura.
Systemic effects	Hypnosis and narcosis accompanied by little or no changes in respiratory and circulatory systems.	Similar to ethyl carbamate.	Similar to hedonal.	No remarkable effects on the circulatory or respiratory systems.	Similar to carbominal.	Same as carbominal.
Doses	Included in U.S.P. Oral 1 to 4 gm.	Dose 1 to 2 gm. orally.	Dose ½ to 1 gm. orally.	Dose: 0.6 to 1.5 gm. orally.	Dose 0.5 to 1.0 gm. orally.	Dose 0.25 to 0.5 gm. orally. Effect lasts five or six hours.
Uses	(1) As anesthetic for laboratory animals. (2) To increase solubility of drugs such as quinine. (3) To depress bone marrow in leukemia. (4) As a hypnotic. Has largely been superseded by barbiturates for human use.	Used as hypnotic and sedative. Use as an intravenous anesthetic is obsolete. Has largely been superseded by barbiturates as a hypnotic for human use.	As sedative and hypnotic. Has largely been superseded by barbiturates.	As a mild hypnotic or sedative. Largely superseded by barbiturates for human use.	As a mild hypnotic and sedative. Little used today in man.	As a sedative and hypnotic. Possesses no analgesic properties.

## HYDROXYDIONE (VIADRIL)

**HISTORY**—Selye (1941) noted that certain steroids (related to the female sex hormones) produced cerebral depression. Since then others have observed similar responses with large doses of steroids. Lauback and associates at the Pfizer Laboratories developed 21-hydroxy pregnane 3,20-dione sodium succinate known as Viadril. The compound is one of many which depresses the nervous system. It is one of the less toxic and has fewer side actions than others which have been studied.

First used clinically by F J Murphy and associates 1956 Investigated by many other clinicians also.

**CHEMISTRY**—The compound is the sodium salt of 21-hydroxy pregnane 3,20-dione hemisuccinate.

**PROPERTIES**—Viadril is a non-volatile water soluble white crystalline powder prepared as a sodium succinate ester. Aqueous solutions have a pH of 7.8 to 10.2.

**Cortex**—Onset of sleep delayed 5-18 minutes. Induction smooth. Devoid of excitement. Not analgesic.

E.E.G. Four patterns: —————

- Pattern I—Increased amplitude 20-40 microvolts, 10-21 cycles per second.
- II—Mixed pattern 5-12 cycles per second, 60-100 microvolts superimposed on low fast activity.
- III—Burst suppression of several seconds duration.
- IV—Widely spaced bursts of less than 20 microvolts or flat tracing.

**Cerebral Blood Flow**—Decreased 25%. Oxygen consumption and glucose uptake depressed.

**Metabolism**—Depressed in large doses.

**Cough Center**—Depressed ————

**Vasomotor Center**—Not appreciably affected.

**Feeding Center**—Not stimulated. Nausea and vomiting due to drug absent.

**Respiration**—Tachypnea. Increased minute volume exchange. Ventilation decreased with large doses.

**Drugs**—Bronchospasm absent. Bronchial reflexes partly obtunded. Permits use of bronchoscopes without inducing spasm.

**Liver**—No appreciable effect. ————

**Detoxification**—Metabolized by liver. Conjugated by enzymatic action on liver 1 pregnane 2,20-diol 21.

**Adrenal**—Effects not known. Drug exerts no hormonal effect.

**Kidney**—Urinary output decreased probably due to decreased blood flow from renal vasoconstriction and release of anti-diuretic hormone. Drug secreted into urine.

**Blood**—No change in morphology of cells.

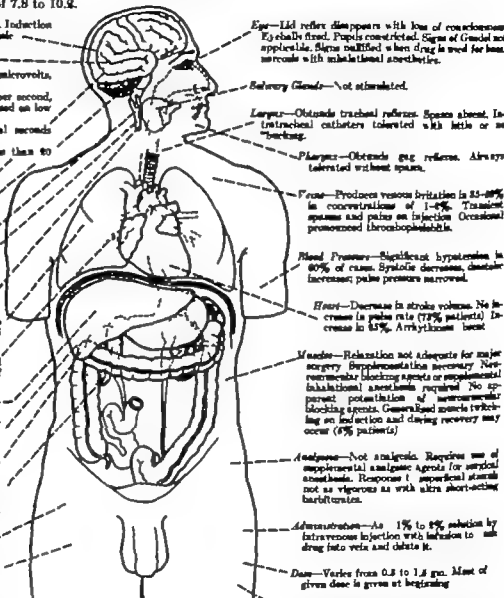
**Fatigue**—Bone marrow changes absent. Excretion may cause inflammation and slough.

## ADVANTAGES

- (1) Non-sparanogenic to bronchi and trachea.
- (2) Greater obtundation of superficial reflexes than occurs with thiopental.

## DISADVANTAGES

- (1) Phlebitis and pain on injection.
- (2) Long latent period.
- (3) Estimated dose must be given in tests for induction. Not as satisfactory if fractionated.
- (4) Hypotension may develop.
- (5) Not analgesic. Requires supplemental analgesics and muscle relaxants.



**Eyes**—Lid reflex disappears with loss of consciousness. Eyeballs fixed. Pupils constricted. Signs of Guedel not applicable. Signs nullified when drug is used for basal narcosis with inhalational anesthetics.

**Salivary Glands**—Not stimulated.

**Larynx**—Obtunds tracheal reflexes. Spasms absent. Intratracheal catheters tolerated with little or no backing.

**Pharynx**—Obtunds gag reflexes. Always tolerated without spasm.

**Venae**—Produces venous irritation in 25-50% in concentrations of 1-5%. Transient spasms and pain on injection. Occasional pronounced thrombophlebitis.

**Blood Pressure**—Significant hypotension in 60% of cases. Systolic decreases, diastolic increases; pulse pressure narrowed.

**Heart**—Decrease in stroke volume. No increase in pulse rate (75% patients). Decrease in 25%. Arrhythmias absent.

**Muscles**—Relaxation not adequate for major surgery. Supplemental is necessary. Neuromuscular blocking agents or supplemental inhalational anesthetics required. No apparent potentiation of neuromuscular blocking agents. Generalized muscle twitching on induction and during recovery may occur (5% patients).

**Analgesia**—Not analgesic. Requires use of supplemental analgesic agents for surgical anesthesia. Response to superficial stimuli not as vigorous as with ultra short-acting barbiturates.

**Administration**—As 1% to 5% solution by intravenous injection with infusion to mix drug into veins and dilute it.

**Dose**—Varies from 0.5 to 1.5 gm. Most of given dose is given at beginning.

**Duration**—Varies from 30 minutes to 1 1/2 hours. Gradual arousal with restlessness. Post-anesthetic circulatory and respiratory depression uncommon.

## USES

- (1) As a basal narcosis in conjunction with nitrous oxide, cyclopropane or non-volatile (aromatic) analgesics.
- (2) For endoscopic procedures when bronchial and laryngeal spasm are possible.

## ATARACTICS (TRANQUILIZERS)

**SYNONYM**—Psychotherapeutic drugs. Also known as normalizers, calmatives, neurosedatives, psychic energizers. Terms are psychological, not pharmacological. The effect, therefore, is produced by a varied group of drugs and not by specific drugs acting at specific sites.

Ordinarily tranquility is accomplished by the use of central nervous system depressants. In certain depressed states, central nervous system stimulants are used.

## I Depressant drugs used are divided into

A Non-selective depressants (analgesics, anesthetics, narcotics and hypnotics)

B Selective depressants. These include

- (1) anti-convulsants.
- (2) anti-histamines.
- (3) muscle relaxants—meprobreson and allied spinal cord depressants.
- (4) central parasympathetic depressants—benactyne, meprotil.
- (5) central sympathetic depressants which act on subcortical areas—phenothiazines and allied drugs.
- (6) sympathetic suppressants—Rauwolfia derivatives.

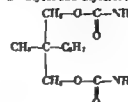
II Central stimulants. These include drugs acting on the cortex and subcortical areas—methylphenidate (Ritalin), pipradrol (Meretran).

## THE CHEMICAL NATURE OF PSYCHOTHERAPEUTIC AGENTS

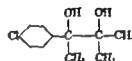
## A. Phenothiazine Derivatives

1. Chlorpromazine is prototype of family of more than a dozen.

## B. Glycol and Glycerol Derivatives



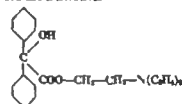
Meprobramate.



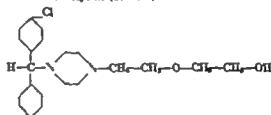
Phenarglycolol (Ultrax)

## C. Rauwolfia Alkaloids—Reserpine (Serpesil)

## D. Diphenylmethane Derivatives



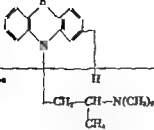

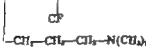
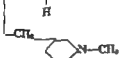
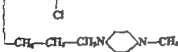
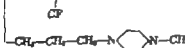
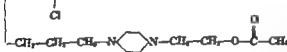
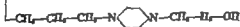
Benactyzine (Benavil)



Hydroxyzine (Atarax)

## SIMILARITIES AND DIFFERENCES OF OTHER PHENOTHIAZINES TO CHLORPROMAZINE

Substitutions on side chain of phenothiazine result in series of chlorpromazine-like compounds similar in pharmacologic properties but varying in potency and toxicity

Name	Chemical	Pharmacology	Toxicity Pattern
Promethazine (Phenergan)		Has diisobutyl group in position N Central depressant. Potent anti-histaminic. Anti-emetic. A mild tranquilizer.	Not as potent as sedative agent. Not as potent as tranquilizer. Dose 25-50 mg.
Promazine (Sparine)		Same as chlorpromazine except it is active in the CL.	Causes jaundice, by potentiation, symptoms of Parkinsonism and similar other side effects as chlorpromazine. Dose 25-50 mg.
Trifluorpromazine (Vesprin)		Has CF <sub>3</sub> in place of Cl in chlorpromazine. 2-8 times more potent than chlorpromazine. More potent anti-emetic.	Less sedation, agitation, motor and hepatic effects. Dose 5-10 mg.
Mepazine (Pacal)		Has an N-methyl 2-piperidinyl methyl group and no chlorine. Anti-emetic tranquilizer of narcotic mild anti-histaminic.	Less hypnotic effect than chlorpromazine. Less effect on liver. Seizures less common. Dose 25-50 mg.
Prochlorperazine (Compazine)		Has N-substituted piperazine ring instead of diethyl amino group. Anti-emetic equal to chlorpromazine. Tranquilizer similar to chlorpromazine.	Drowsiness. Some hypotension. Less hepatic and bone marrow effects. Dose 5-10 mg.
Trifluorperazine (Stelazine)		Has CF <sub>3</sub> in place of Cl in prochlorperazine. Ten times more potent. One-tenth as active in potentiating barbiturates.	Similar to chlorpromazine. Fewer side effects. Dose 5 mg.
Thiopropazine (Dactal)		Has N-substituted piperazine group instead of diethyl amino group. More potent than chlorpromazine.	Toxic manifestations not increased in proportion to potency. Dose 5-10 mg.
Perphenazine (Trilafon)		Has N-substituted piperazine ring instead of amino group. More potent than chlorpromazine.	Toxic manifestations less than chlorpromazine. Dose 4-8 mg.

## CHLORPROMAZINE (THORAZINE)

**HISTORY**—Phenothiazine derivatives first synthesized by Bernthsen (1893). French investigators noted sedative effects in 1945. Laborit (France) promethazine (Phenergan) to supplement nitrous oxide anesthesia. Charpentier synthesized chlorpromazine 1950.

**SYNONYMS**—Thorazine, Largactil.

**CHEMISTRY**—Chlorpromazine is 2, chloro, 10 (dimethylaminopropyl) phenothiazine. Forms a salt with hydrochloric acid which is a grayish white powder soluble in water, acid in reaction (pH 5). Solution turns brown on exposure to light. Must be stored in light proof containers. Powder stable.

**Cortex**—Reduces motor activity of hyperactive patients. Single doses do not alter ability of normal subjects to perform psychologic tests. Produces state of sleep different from general anesthesia from which subject may be aroused.

No direct effect on cortex by single doses. E.E.G. not altered. Does not alter spontaneous or evoked burst discharge or cortical changes.

Antagonizes psychomotor effects of caffeine, naltrexone and other stimulants. Not an anti-convulsant. Does not abolish electrically induced seizures.

**Basal Ganglia**—Toxic responses produce a reversible Parkinson-like syndrome. Develops after prolonged, sustained high doses. May cause severe changes.

**Reticular Activating System**—Causes depression of ascending reticular activating system, produces somnolence.

**Diencephalon**—Depresses seat of autonomic system.

**Forming Center**—Potentile Amino Acids centrally. Suppresses vomiting due to central acting chemical agents, such as apomorphine.

**Heat Regulating Center**—Depressed if combined with narcotics or hypnosis. Body temperature tends to approach that of environment.

**Lungs**—Large doses depress respiration. Reduces depression caused by hypnosis by potentiating effect which reduces dose of hypnosis or narcotic necessary.

**Liver**—Produces obstructive type jaundice. Appears to be dosage related. More common in higher dose than sustained administration.

**Detoxification**—None recovered in urine. May appear as metabolite. Chlorpromazine, metabolite similar in pharmacologic properties as chlorpromazine but less active.

**Kidney**—N appreciable changes caused by drug.

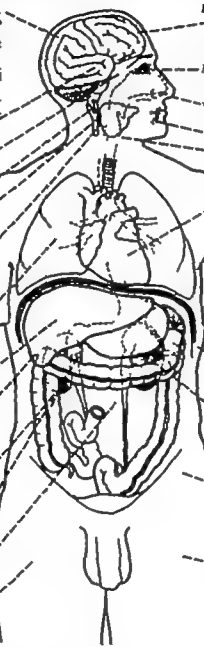
**Adrenal**—Exerts an anti-adrenergic and anti-adrenergic effect. Prevents release of A.C.T.H. and release of gonadotropic hormone. Endocrine functions also depressed due to direct suppression of diencephalon.

**Spinal Cord**—N appreciable effect on either monoaminergic or polyaminergic mediated reflexes.

**Peripheral Nerve**—Does not change potential evoked by single stimuli. Possesses some local anesthetic activity.

**DOSAGE**—After oral administration effects apparent in 1 hour, peak reached in one hour. Lasts several hours. Effective orally. Irritating subcutaneously. Intravenous dose may cause circulatory collapse. Doses must be individualized. Varies from 30-90 mgm.

**CONTRAINDICATIONS**—1. Marked central nervous depression. 2. Liver disease. 3. Surgery or anesthesia in patients with cardiovascular disease, hyperkalemia, anemia. 4. Hypothyroidism. 5. Adrenal insufficiency.



**Potential of Sedation**—Increases sleeping time of most hypnotics. Enhances the effects of ether. Possesses only a slight analgesic activity but enhances the effects of true analgesics, permitting control with smaller doses.

**Eyes**—N appreciable changes in single doses or if drug is used alone. Lid reflex remains intact. Corneal reflex remains intact.

**Nose**—May cause nasal stuffiness, dry mouth. Possesses mild antihistaminic activity. Much less than promethazine.

**Pharynx**—No changes.

**Larynx**—No changes.

**Heart**—Tachycardia may follow large doses. No appreciable effect on myocardium. No electrocardiographic changes. Tends to suppress arrhythmias. Causes coronary vasodilation. Antagonizes arrhythmias produced by epinephrine with hydrocarbon anesthetics.

**Blood Pressure**—Abolishes pressor response to stimulation of the vagus. Causes orthostatic hypotension. More common following paravertebral use after the use of general anesthesia or surgery. Severe fatal peripheral circulatory failure may occur after intravenous administration.

Prevents pressor response to epinephrine and norepinephrine.

**Body Temperature**—Falls. Due to (1) sym patholytic action of drugs resulting in peripheral dilatation, (2) reduction in muscle activity (3) cold external environment and (4) inactivation of heat regulating center.

**Gastro-intestinal**—No significant effects. Large doses may cause gastric irritation and reduce gastric secretion. No appreciable effect on smooth muscle when used alone.

**Muscle**—Decreases response to both direct and indirect stimulation. Does not act at myoneural junction.

**Skin**—May cause eruptions due to contact dermatitis. May also cause photosensitization.

**Bone Marrow**—May produce agranulocytosis, aplastic anemia or pancytopenia.

**Autonomic Nervous System**—Produces a ganglionic depressant effect. Partly responsible for hypotension.

**Arterioles**—Causes relaxation of vascular bed due to sympatholytic effect.

**Tissues**—Leaves blood quickly. Highest concentrations in brain. Lowest concentration in lungs, spleen, kidney liver.

**USES**—1. As tranquilizer for mental diseases. 2. To potentiate narcotics, hypnotics, and anti-convulsants. 3. As an antiemetic. 4. To depress the heat regulating center.

**OBJECTIONS**—1. Causes difficult to reverse hypotension, particularly during operation and surgical anesthesia. 2. Suppresses reflex activity. 3. May cause jaundice. 4. May cause liver



## SEDATIVES AND HYPNOTICS

Name	Meprobamate	Hydroxyzine	Ethiazams	Ethchlorvynol	Methyprylon
Synonym	Miltown, Equanil	Atarax, Vistaril	Valmid	Flacidal	Noctadar
Chemistry	Carbanic acid ester of 2, methyl 2, 5-propyl, 1,3 propandiol.	1(p-chlorobenzyl hydroxy-4 (2-2 hydroxy ethoxy ethyl) piperazine.	1,ethynyl cyclohexyl carbamate	A halogenated triple bonded alcohol. Has triple and double bonded and saturated side chains on methanol. Beta chlor vinyl ethynyl, ethyl carbamate.	2,3 dimethyl 5, methyl, 2,4 piperidinedione
Properties	Chemically allied to meprobamate. Stable white powder M.P. 103°C. Poorly soluble in water.	Forms a hydrochloride.	White powder	Stable.	Stable, white powder
Major actions	As a central muscle skeletal relaxant. Anti-convulsant. Antagonizes methanol and strychnine convulsions.	Some tranquillizing effect similar to phenothiazines. Sedation.	Sedative and hypnotic.	Sedative and hypnotic. Non-analgesic.	Hypnotic and sedative. Not an analgesic.
Sites of action	Depresses intervertebral neurons in cord. No effect on monoaminergic neurons. Suppresses thalamus.	Some cortex, possibly mid-brain.	Non-specific. Act on cortex like barbiturates.	Non-analgesic. Acts on cortex. Produces additive effect with other hypnotics. Daytime sedative.	Cerebral cortex. Similar to barbiturates. Not much different in response. Daytime sedative.
Side actions	Not anticholinergic. Produces no autonomic effects. Does not act at synapses or junctions.	Slightly antihistaminic. No sympatholytic effect.	Non-analgesic.	Hangover effect noted. No effects on liver kidney or bone marrow.	No effect on liver, kidney or bone marrow.
Toxic effects	Large doses depress centrally. Wide margin of safety.	Toxicity low. No hepatic effect. Does not depress bone marrow.	Respiratory depression is sensitive doses.	Overdosage results in respiratory failure.	Overdosage results in respiratory failure.
Elimination	10% unchanged, 90% conjugated as glucuronide.		Completely metabolized probably by hydrolysis.	Undergoes detoxification in liver. Bile renal excretion does not enhance duration.	Dehydrogenated to tetrahydropridone which may be toxic to bone marrow.
Dose	Used orally. Intravenously causes thrombosis, hemolysis.	Used as daytime sedative for symptomatic management of neuritis.	300 mgm. orally as hypnotic.	300 mgm. Onset 30-60 minutes. Lasts 4-8 hours.	30-100 mgm. orally for hypnosis.

# SECTION X. OPIUM ALKALOIDS AND SYNTHETIC ANALGESICS

## THE OPIUM ALKALOIDS

Opium is the dried resinous exudate derived by incising the unripe capsule of *papaver somniferum* (opium poppy). The plant is found in Asia Minor, China and certain Mediterranean areas.

### SOLUTIONS

**Tincture**—10% solution in alcohol (1 cc.=0.1 gm. opium = 10 mgm. morphine)

**Comphorated tincture**—1/25 (1 gm.) of amount of opium in the tincture plus camphor (1 gm.) benzoic acid (1 gm.) and oil of anise (1 cc.) per liter of 10% alcohol.

**Pentamum**—Solution of total alkaloids of opium in form of hydrochloride. 1/10th of weight of alkaloids is morphine



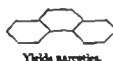
Opium Powder Contains

alkaloids  
pectin  
sugars  
salphates  
lactates  
mucous acid

Powder

U.S.P.: 10% consists of alkaloids by weight.

### Phenanthrene Group



Yields narcotics.

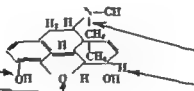
Yields approximately 25 alkaloids.  
Divided into two groups.

### Isophanoline Group (Papaverine most important)



Phenolic hydroxyl group determines narcotic potency

Ethereal oxygen is inert.



Tertiary N gives basic properties, forms salts with acids.

OH not phenolic due to partial hydrogenation of ring—responsible for convulsive effects.

Alteration of ether hydroxyl of morphine alters narcotic or convulsive effect.

Methylation of phenolic hydroxyl decreases potency



Both hydroxyls methylated results in diacetyne (convulsant)



**Morphine (U.S.P.)**  
Intensity of action, duration of action, and analgesic effect most pronounced of whole group habit-forming.

**Codeine (U.S.P.)**  
Least potent, dose required 4 to 8 times that of morphine—habit-forming.

Ethylation of phenolic hydroxyl decreases potency. Produces diacetyne



**Diacetyne**  
Action equivalent to codeine

Both hydroxyls acetylated, narcotic effect enhanced approximately six times.



**Heroin**  
Short, intense action; less side effects than with morphine—habit-forming.

Phenolic hydroxyl intact



Hydrogenation of double bond in ring 3, and conversion of hydroxyl to ketone group.



**Dilaudid (N.N.R.)**  
Less convulsant as analgesic as morphine 10 times more toxic than morphine—habit forming.

Phenolic hydroxyl methylated



Same as in dilaudid.



**Diacidid**  
Less intense action than dilaudid.

Phenolic hydroxyl intact



Same as dilaudid except one hydrogen on ring 3 has methyl group.



**Metopon**  
Less hypnosis but has equal analgesic potency as morphine

## MORPHINE

**HISTORY**—Isolated from opium by Serturner in 1805

**Cerebrospinal Axis**—Pretibial central stimulation often causes excitement, followed by depression. Descending depression occurs.

**Temperature Regulating Center**—Depressed.

**Respiratory Center**—Depressed; threshold of cells  $\uparrow$   $\text{CO}_2$  increased; discharge of rhythmic impulses slowed

**Vasomotor Center**—No change. Toxic doses depress.

**Forming Center**—Stimulated. Nausea and vomiting common.

**Cough Center**—Depressed. Large doses abolish reflex.

**Papae Center**—Stimulated. May cause slowing of pulse.

**Cerebral Striae**—Depressed.

**Brain-cortex Chemosensory**—Remains active

**Lungs**—Respiratory rate decreased, tidal exchange slightly increased, minute volume exchange decreased.  $\text{CO}_2$  output decreased, total blood  $\text{CO}_2$  and alveolar blood  $\text{CO}_2$  increased. Bronchial musculature constricted. Redness, clinical dyspnea by depressing vagal reflexes by reducing central perception.

**Metabolism**—Rate decreased 10%.

**Adrenal**—Epinephrine content depleted with large doses (anemia)

**Gallbladder**—Smooth muscle tone increased. May enhance biliary spasm. Atropine antagonizes spasm.

**Liver**—Function decreased for six hours (dye test). Glycogen depleted due to release of sympathin. Hypertrophy of little significance except with large doses.

**Kidney**—Function not significantly affected; oliguria, followed by polyuria may occur.

**Uterus**—Smooth muscle spasm occurs increased tone, decreased motility. Relieved by atropine.

**Bladder**—Urine retention may follow due to spasm of sphincter.

**Sphincters**—Tone increased and defecation reflex obliterated.

**Autonomic Effect**—May behave like parasympathetic stimulant. Effects enhanced by prothigina.

**Card**—Stimulated.

**Peripheral Nerve**—Not affected; hyperactive reflexes from stimulation of cord may result. No local anesthetic action.

**PROPERTIES AND PREPARATIONS**—An organic base. It is a white powder composed of fine needles which darken on exposure to air. One gram dissolves in 8000 cc water. It forms salts with many organic and mineral acids, most important of which is the sulphate. The sulphate is a white powder soluble in water (1 in 18.5 at 25°). It is partly soluble in alcohol and insoluble in chloroform and ether. Morphine is included in the U.S.P. XIII.

**Cortex**—Psychic stimulation decreases of time sense merging into dreamlike sleep. Threshold to pain perception raised. Removes psychic response to pain. Pain paths to consciousness interrupted. Motor areas unaffected by small doses, depressed by large doses. Perception and will unaffected. Deep coma with overdose.

**Intracranial Pressure**—Increased. Respiratory depression with asphyxia further increases it.

**Optic Thalamus**—Analgesia. Dull pain obliterated. Large doses abolish all pain including visceral.

**Eyes**—Pupils constricted due to stimulation of motor (Edinger Westphal) nuclei. Dilate with asphyxia, active retinal movements. Reflex remains active if antagonized by atropine.

**Salivary Glands**—Secretion decreased due to interference of reflex stimulation of gland.

**Heart**—Rate decreased (vagal); P R interval increased, no action on myocardium; rarely slight stimulation may occur.

**Blood Pressure**—Affected only slightly with therapeutic doses. Usually reduced due to psychic sedation. May fall following postural changes due to depression of compensatory mechanisms.

**Stomach**—Motility decreased; emptying time increased; secretion of acid decreased, drug excreted in stomach.

**Intestines**—Activity decreases: passage of chyme through bowel slowed. Bowel tone decreased. Absorption little affected. Spasms and constipation frequent. Water more completely absorbed from the chyme.

**Pneumonia**—Secretions diminished.

**Uterus**—Tone increased and contractions usually decreased. Drug passes through to fetus and often results in neonatal spasm.

**Skeletal Muscles**—Not affected. Stored temporarily in muscle. Muscle coordination not affected (motor cortex not depressed).

**Blood**—Coagulating power decreased. Lactic acid increased. Anticoagulant for 84 hours. Marked depression if alkalosis is present.

**Body Temperature**—Falls due to depressed center. Dilated skin vessels and reduced metabolic rate.

**Skin**—Peripheral vessels dilate. Itching of nose may occur. Urticaria not uncommon. Sweating common. Not absorbed through unbroken skin.

**Tolerance**—Develops after repeated administration for 10 days to two weeks, necessitating larger doses to obtain desired therapeutic effect.

**Addiction**—Follows habituation and development of tolerance.

**Excretion**—10 to 15% eliminated unchanged in four or five hours. Stored temporarily in muscles. Remainder excreted by liver and excreted into urine in 84 to 96 hours. Traces found in urine, feces, and stomach contents. Intravenous dose disappears in 10 to 80 minutes from blood. Stored in tissues.



OPIMUM ALKALOIDS AND THEIR DERIVATIVES

	Codaine	Heroin	Dihydrocodone	Duane	Metopon	Papaverine	Apomorphine
History	Isolated by Reubens in 1824.		Introduced by Krich in 1898.		Developed by drug addiction commission.		
Chemistry	Methyl morphine occurs naturally like made by methylation of morphine.	Diacetyl morphine. Made synthetically by acetylation of morphine.	Dihydromorphine	Ethyl morphine. Prepared synthetically by ethylation of morphine	A synthetic substance made from morphine. Methyl dihydromorphine	Derived from opium. Contains no pharmacotherapeutic, 1 an antispasmodic derivative.	Made by dehydration of morphine by heating with hydrochloric acid. Molecular rearrangement occurs.
Analytical action	One-fourth of morphine.	Four to eight times as potent as morphine.	Ten times more potent than morphine.	Similar to codaine.	It is as potent and similar to morphine but of shorter duration.	None	Unstable
Narcotic action	Mild. Large doses may even cause excitement. (See above) refers more than morphine	Causes euphoric excitement. Four to six times more depressing than morphine.	Four times more potent than morphine. Lasts shorter than morphine.	Similar to codaine.	Less dulling of respiration than with morphine.	None	Hypnotic in small doses. Produces no additive effect with other depressant
Morbidities	Slightly reduced. Increased by large doses.	Reduced more than with morphine.	Similar to morphine in comparable doses.	Similar to codaine.	Similar to morphine.	Flight. May increase in large doses.	
Respiratory effects	Approximately one-fourth as potent as morphine in causing depression.	Over four or five times more depressing than morphine.	Similar to morphine in comparable doses.	Similar to codaine.	Little or no depression of respiration.	None. Little or no effect in reduction of bronchial secretions.	Large dose causes collapse.
Circulatory effects	No remarkable effects.	Similar to morphine.	Similar to morphine in comparable doses.	Similar to codaine.	Similar to morphine but less active.	None. Relieves smooth muscles of blood vessels. Dilates coronary.	Large dose may cause collapse.
Effects in gastro-intestinal tract	Causes spasm, constipation, etc. but less pronounced than morphine.	Similar to, but considerably less than morphine in proportionate doses.	Similar to morphine in comparable doses but less emetogenic	Similar to codaine.	Similar to morphine but less active.	Relieves smooth muscles.	Not irritating. Causes cramps by central stimulation.
Reflex tract	Spasm of bile duct similar to morphine but is as short and intensity		Spasm of bile duct but less intense in onset and intensity	Similar to codaine.		Relaxes smooth muscles.	
Cardiac and bladder	Increased tone, decreased activity	Similar to morphine in proportionate doses.	Similar to morphine in comparable doses.	Similar to codaine.		Relaxes smooth muscles.	Probably none.
Cerebrum	Depresses non-specifically. Low than morphine.	Similar to morphine in proportionate doses.	Similar to morphine in comparable doses.	Similar to codaine.		None.	None.
Other response	Effects on vision less pronounced than with morphine	Similar to morphine in proportionate doses.	Similar to morphine in comparable doses.	Similar to codaine.	Less than morphine.	None.	None.
Excretory action	Prevent but less than with morphine	Less than morphine in proportionate doses.	Similar to morphine in comparable doses.	Similar to codaine.	Less than morphine.	None.	Prevented action. Musculars vomiting center
Antispasmodic action	Prevent but less than with morphine.	More effective than morphine.	Similar to morphine in comparable doses.	Similar to codaine.	Similar to morphine.	None.	None.
Chemical action	Approximately 80% unchanged excreted into urine.	Mostly unchanged unchanged in urine.		Similar to codaine.			Fluorinated unchanged.
Toxicology	Occurs with repeated administration	Readily occurs with repeated administration.	Readily occurs with repeated administration.	Readily occurs with repeated administration.	Partly occurs with repeated administration. Less addiction symptoms of morphine.	None.	None.
Addiction	Occurs. Large doses required to produce addiction.	Most addictive of morphine-like drugs.	Causes physical dependence. Less euphoric than with morphine.	Produces mild addiction symptoms.	Mild addiction properties. Less addiction than most opium derivatives.	None.	None.
Preparation	Codine (official) U.S.P. XIII. Codone (official) U.S.P. XIII. Tablets and white 1.30 H <sub>2</sub> O. Codone phosphate (white 1.8 H <sub>2</sub> O) (for injection)	Diacetyl morphine hydrochloride. Not legal to manufacture or import into the U.S. Not official.	Dihydromorphine U.S.P. Prepared as the hydrochloride, white crystalline or crystalline water-soluble powder	White powder prepared as hydrochloride. Not official.	White powder prepared as hydrochloride. Not official.	White powder prepared as hydrochloride. Included in U.S.P. XIII.	Included in U.S.P. XIII.

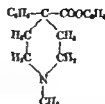
All foregoing drugs under supervision of Harrison Narcotics Act.

# DEMEROL

**HISTORY**—Synthesized by Eisleb and Schaumann in Austria in 1939 as a substitute for atropine. An analgesic, spasmolytic and mild sedative agent.

**SYNONYMS**—Meperidine, Isompeccine, dolantin, pethidine.

**CHEMISTRY**—A synthetic derivative of piperidine, (1-methyl, 4-phenylpiperidine 4-carboxylic acid ethyl ester) possessing the following structure



**Cortex**—Euphoria followed by mild depression. Rarely produces sleep. Tolerance may follow repeated use of drug. Addiction liability less than morphine but present nevertheless. Drowsiness or sleep occurs with large doses. Dizziness and giddiness common as a side reaction.

**Respiratory Center**—Mild depression with sedative doses. Massive doses cause respiratory failure.

**Cough Center**—Not depressed. Slight or no antitussive action.

**Vomiting Center**—Nausea and vomiting may follow rapidly injected intravenous doses or in ambulatory subjects. Nausea and vomiting common in small number of cases regardless of route of administration.

**Vagus**—Depressed. Drug possesses a mild atropine-like action.

**Lungs**—Little or no change in ventilation. Respiration depressed by large doses. Usually causes broncho-dilatation. No effect on blood.

**Gallbladder**—Spasmolytic action. May be useful in spasm of biliary ducts.

**Uterus**—Spasmolytic action causes decreased tone. Direct depressant action on muscles reduces spasm.

**Bladder**—Urinary retention uncommon.

**Skin**—Pallor and sweating may occur as side reaction.

**Blood**—No change in hematopoietic system. No notable blood chemical changes.

**Intracranial Pressure**—May increase. Slight pallor and depression of respiration occur in presence of intracranial lesions.

**Thalamus**—Causes analgesia. Potency approximately 1/10th of action of morphine. Potency less between codeine and morphine.

**Eye**—Size of pupil unchanged. Blurring of vision occurs as side reaction. Dilatation of pupil with large doses.

**Salivary Gland**—Moderate decrease in secretions. Dryness of mouth may occur as side reaction. Not as effective as atropine. Does not replace atropine in preanesthetic medication.

**Heart**—N effect in therapeutic doses. No changes in electrocardiogram. Pulse rate unchanged or increases slightly following therapeutic doses.

**Blood Pressure**—Usually no notable effect. Transient hypotension may follow rapid intravenous administration. Probably due to peripheral vasodilation. No effect otherwise.

**Spleen**—Volume increased.

**Stomach**—Spasmolytic action. Brisk gastric peristalsis. Delays gastric emptying time 80%.

**Intestines**—Decrease in motility due to spasmolytic action. Depresses smooth muscle fibers. No constipating effects. Does not spasm bowel.

**Throat**—No appreciable reduction in activity or tone. Drug passes into placental circulation. Large doses cause depression of fetal respiration.

**Side Reactions**—Frequent. Dizziness, nausea, vomiting, pallor. More frequent in ambulatory subjects.

**Elimination**—Mostly unchanged. Approximately 75% of a therapeutic dose recovered in urine six to seven hours after administration.

## CLINICAL USES

As an analgesic orally 100 to 180 mgm. Intramuscularly 80 to 100 mgm. Intravenously 80 to 100 mgm. slowly (side reactions frequent). Clinical use governed by Federal Bureau of Narcotics. The drug causes addiction.

**ONSET OF ACTION**—Twenty to thirty minutes. Analgesic potency less between that of codeine (80 mgm.) and morphine (15 mgm.). Widely used as an effective analgesic combination with barbiturate and propofol.

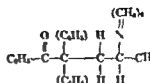
**PREPARATION**—Demerol is a white crystalline substance slightly soluble in water with a strong alkaline reaction. Forms salts with mineral acids.

For clinical use the hydrochloride is employed. It is a white crystalline powder soluble in water melting at 187°. Not decomposed by boiling.

# METHADON

**SYNONYMS**—Adanon, analone dolophine amdon.

**CHEMISTRY**—An aliphatic amino ketone (8 dimethyl amino-4,4 diphenyl-3 heptanone synthesized by the Germans during World War II. It is a synthetic basic compound which forms salts with acids. The most common salt is the hydrochloride. Its formula is



**Center**—No significant effect. Large doses (10 mgm.+) cause depression. Does not allay apprehension. Euphoria with large doses. No effect on electroencephalogram. Large doses depress cause slowing of cortical activity

**Respiratory Center**—Depressed by moderate and large doses

**Thyroid Center**—Stimulated. Slows the heart

**Feeding Center**—Nausea and vomiting occurs as side reaction particularly with large doses

**Cough Center**—Depressed Acts as antitussive

**Vagus Nerve**—Causes hyperactivity which is antagonized by tropine

**Lungs**—Mixed volume exchange reduced approximately 18% with therapeutic doses.

**Liver**—Cephalic circulation, blood bilirubin remains unchanged after successive daily doses

**Kidney**—Urinary output reduced. Antidiuretic action lasts several hours.

**Uterus**—Spasmodic action. Caused by parasympathetic action

**Blood**—No change in blood sugar or %P.N. No effect on total number of morphology of W.B.C. or R.B.C. Total counts unchanged over prolonged periods of administration

**Elimination**—Approximately 85% of 7.5 mgm oral dose eliminated unchanged. Remainder detoxified. Exact fat not known

**PHYSICAL PROPERTIES**—White crystalline substance soluble in water and alcohol, insoluble in ether melts at 230 to 235°C. Possesses a bitter taste.

**Thalamus**—Increase in pain threshold

**Eye**—Miosis in large doses.

**Salivary Glands**—Stimulated. Secretions may be increased.

**Heart**—Pulse rate slowed. E.K.G. shows some bradycardia and prolongation of QRS Complex (vagal effect) Abolished by atropine.

**Blood Pressure**—No effect or slight lowering of systolic pressure.

**Intestine**—Increases muscle tone. Propulsive activity decreased. Spasmodic action caused by parasympathetic stimulation. Locally causes a spasmodic action.

**Uterus**—Drug passes through placenta. Fetal respirations depressed.

**Addiction**—Relieves the morphine abstinence syndrome in addicts. Tolerance develops after prolonged administration followed by withdrawal symptoms.

## CLINICAL USES

**For Preoperative Medication**—Does not allay apprehension. Useful only when combined with sedatives such as barbiturates.

**For Postoperative and Other Pains**—As narcotic comparable to morphine in potency

**Dosage**—Oral 2.5 to 10 mgm—average dose 5 mgm—effect becomes established within 30 to 60 minutes. Intramuscularly 1 to 10 mgm. Effect becomes established within 30 to 60 minutes Intravenously 2.5 to 10 mgm. Effect becomes established within 5 minutes.

## SYNTHETIC NARCOTIC ANALGESICS

Name	Levorphanol	Alphaprodine	Asulfone	Phenazone
Synonym	Dromoran, Levo-dromoran	Nuorfin	Larodin	AN-695 NIT-9919, Promadol
History	Introduced in 1944	Prepared by Randall & Johnson 1949	Prepared by March 1957	Synthesized by E. L. May (Kathel Institute of Health U.S.A. 1957)
Chemistry	1-4 hydroxy N-ethyl morphine. Lacks oxygen bridge, alcoholate hydroxyl group and double bond between carbons 7 & 8 of morphine. Has 4 & 5 bars	1,4-dimethyl 6-phenyl 6-phenylidene morphine. Allied to morphine except has propenyl group instead of saturated tertiary linkage. Forms hydrochloride.	Similar to morphine except absence of carbonyl $\text{C=O}$ and $\text{NH}$ group. Instead of $\text{NH}$ , forms phosphite instead of hydrochloride. $\text{Phenyl} / (4\text{-methyl } 6\text{-phenyl isopropoxide})$	6-hydroxy 2, 6 dimethyl 2-phenyl ethyl 1-4-7 isomorphine. White powder M.P. 104°-105°C. D & L form. $\text{NaCl}$ forms active. Levo 60% potent than dextro.
Analgesic action	Levo continuous active, dextro not. 4-8 times more potent than morphine. Maximal effect in 1-1 1/2 hrs. Lasts 4-8 hrs.	Shorter acting but more intense effect than morphine but less than morphine.	Intermediate between morphine and morphine. 1/2 (more greater than morphine, 1/2 no potent as morphine.	5 to 10 X more potent than morphine
Narcotic or hypnotic action	4-8 times more potent than morphine. Hypnotic effect not seen in presence. Dextro seems to effect. Offers little or no advantage over morphine.	Less intense than and shorter acting than morphine.	Less than morphine. Similar to morphine. Duration approximately 4 hrs.	Less than morphine. Excellent sedative. K.S.G. pattern similar to normal sleep.
Effects on respiration	Depresses similar to morphine in comparable doses. Antagonized by naloxone or levorphanol.	Depresses but less than morphine. Antagonized by naloxone or levorphanol.	Depresses respiration more than morphine but less than morphine. Causes fatal depression. I.V. administration of 10 mg. or more causes apnea. Antagonized by morphine and levorphanol.	Shows none. Depressed but not to same extent as morphine. Some depression in tidal volume in 8 mgm. dose.
Cardiac effects	Similar to morphine in comparable doses.	Similar to but less intense than morphine.	Hypotension follows rapid I.V. injection or administration.	Some bradycardia. Some effects as morphine but less cardiac output. Not depressed.
Gastrointestinal effects	Similar to morphine in comparable doses	Similar to morphine-spasmodic.	Spasmodic effect like morphine. Opposite to morphine.	
Biliary tract	Similar to morphine	Similar to morphine.	Similar to morphine.	
Urinary effects	Similar to morphine.	Similar to morphine.	Similar to morphine.	
Uterus	Similar to morphine	Passes into fetal circulation.	Similar to morphine. Some slowing of labor	Passes through placental barrier
Ocular response	Similar to morphine	Similar to morphine.	Similar to morphine.	
Kinetic effect	Qualitatively similar to morphine. Quantitatively less.	Does not cause intense sedation as morphine.	Ordinarily not seen except in combination.	None. Even less an anti-emetic effect.
Antagonistic effects	Similar to morphine. Dextro derivative active also.	Similar to morphine.	Possesses an anticholinergic effect.	
Fluorination	Conjugated in liver 15-60% excreted in glucuronide slowly (5-6 days).	Completely excreted in body	Partly excreted by liver and partly eliminated unchanged.	Antagonized by morphine.
Tolerance and addiction	Similar to morphine. Tolerance develops as rapidly. Coder Barrow-Nuorfin Low	Tolerance develops. Addiction liability less than morphine. Coder Barrow-Nuorfin Low	Tolerance develops after repeated doses. Addiction liability equivalent to morphine. Suppresses morphine tolerance completely. Morphine does not. Does equivalent to morphine tolerance reduction.	Appears to have addicting qualities but less than morphine.
Preparation	5 mgm. tablets or 2 mgm. per cc. for I.M. use. Dose 5-10 mgm	50-100 mgm. I.M. May be used orally I.V. Not used orally	50-100 mgm. I.M. Effective orally 20-75 mgm. Duration 3-8 hrs.	Stoche 10 cc. 1.0 mgm./cc. Dose 5 to 8 mgm. I.M. Dose 5 to 8 mgm. I.V.

# ANTINARCOTICS—NALORPHINE (NALLINE)

**HISTORY**—Synthesis and pharmacologic actions first described in 1942 by Weijlard and Erickson. Hiller (1943) and also Unna noted that the compound antagonized the action of morphine in animals. Hart and McCauley (1944) reported additional studies confirming Unna's findings. Huggins and co-workers (1950) and Smith, and Lehman reported experimental studies in man. Possibility that an antidote might be found first indicated by Pohl (1914) who noted that N-allyl-nor-codeine antagonized morphine.

**DESCRIPTION**—Chemical name is N-allyl-normorphine. Nalorphine is a congener of morphine. A methyl group on the nitrogen atom is replaced by an allyl group. The drug is not a stimulant or convulsant. It is a narcotic far more feeble than morphine.

**Central**—Used alone exhibits a mild hypnote effect. Does not restore consciousness. Debits depression of respiration, dysphoria and hallucinations. F.E.G. Does not restore to awake pattern. May over slow vams.

**Analgesic Action**—Alone has analgesic potency equal to or nearly equal to morphine. Not satisfactory for pain relief due to side actions.

**State of Consciousness**—Patients become more responsive to external stimuli. Awakening does not occur (except in addicts).

**Eye**—Causes constriction of the pupils. Used in combination with morphine in overdose it relaxes pupil.

**Cough Center**—Exerts an anti-tussive effect equal to codeine. Not used for this purpose. Exerts additive effect with that of morphine and codeine.

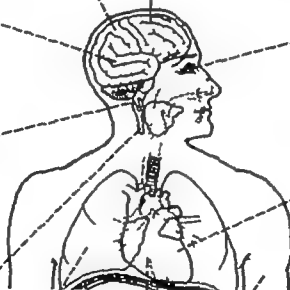
**Heart**—No circulatory effects observed.

**Respiratory Center**—Sensitivity to carbon dioxide restored after depression due to morphine.

**Blood Pressure**—No significant changes. Restores blood pressure reduced to normal state.


**Lungs**—Minute volume exchange increased a average of 85% in narcotic depressed patient. Mild depression if used alone. Restores response of respiratory center to CO<sub>2</sub> when depressed by morphine.

**Pulse Rate**—Slight but significant slowing in cardiac rate.





## SYNTHETIC NARCOTIC ANALGESICS

Name	Levorphanol	Alphaprodine	Anileridine	Phenazocine
Synonym	Dromoran, Lero-dromoran	Nimezil	Loridine	AN-6968, NIM-7315, Promidol
History	Introduced in 1964.	Prepared by Radeff & Lohmann 1962	Prepared by March 1967	Synthesized by E. L. May, National Institutes of Health U.S. 1967.
Chemistry	1-6 hydroxy N-acetyl morphine. Lacks ether bridge, alcohols hydroxyl group and double bond between carbons 7 & 8 of morphine. Has 4 & 5 form.	1,5-dimethyl 6-phenyl 6-phenylidyl propionate. Alkyl to morphine except has propionate group instead of esterified ether bridge. Forms hydrochloride.	Similar to morphine except nitrogen atom bears $\text{-C}_6\text{H}_4\text{-}$  $\text{-NH}$ group instead of $\text{NH}$ . Forms phosphate instead of hydrochloride. Ethyl 11(6-methyl 6-phenyl) isomorphine.	1,6-dihydroxy N, 9 dimethyl 6-phenyl 6-phenyl 11(6-methyl 6-phenyl) isomorphine. White powder M.P. 136°-4°C. D & L form. Both forms active. Loro 60X potent than dextro.
Anesthetic action	Loro composed action, dextro not. 6-8 times more potent than morphine. Maximal effect in 1-1 1/2 hrs. Lasts 6-8 hrs.	Shorter acting but more intense effect than morphine but less than morphine.	Intermediate between morphine and morphine, 11 times greater than morphine, 1/2 as potent as morphine.	1 to 10X more potent than morphine.
Narcotic or hypnotic action	6-8 times more potent than morphine. Hypnotic effect not quite as pronounced. Dextro same as effect. Others little or no advantage over morphine.	Less intense than and shorter acting than morphine.	Less than morphine. Similar to morphine. Duration approximately 4 hrs.	Less than morphine. Excellent sedation. E.E.G. pattern similar to normal sleep.
Effects on respiration	Depresses similar to morphine in compatible dose. Antagonized by naloxone or levorphanol.	Depresses but less than morphine. Antagonized by naloxone or levorphanol.	Depresses respiration more than morphine but less than morphine. Central depression. L.V. administration of 70 mg. or more causes apnea. Antagonized by morphine and levorphanol.	Slows rate. Depressed but not as much as morphine. Some decrease in tidal volume in 2 mg. dose.
Circulation effects	Similar to morphine in compatible dose.	Similar to but less intense than morphine.	Hypotension follows rapid L.V. injection or subcutaneous.	Some bradycardia. Some effects on morphine but less marked output. Not depressed.
Cardiovascular effects	Similar to morphine in compatible dose.	Similar to morphine-sympathomimetic.	Spasmodic effect the morphine. Opposite to morphine.	
Motor effect	Similar to morphine.	Similar to morphine.	Similar to morphine.	
Urinary effects	Similar to morphine.	Similar to morphine.	Similar to morphine.	
Diuresis	Similar to morphine.	Prevents renal excretion.	Similar to morphine. Some slowing of labor.	Passes through placental barrier
Ocular response	Similar to morphine.	Similar to morphine.	Similar to morphine.	
Emetic effect	Qualitatively similar to morphine, quantitatively less.	Does not cause unless subcutaneous or oral.	Ordinarily not seen except in emetic doses.	None. Even less an anti-emetic effect.
Antitussive effects	Similar to morphine. Dextro derivative more active.	Similar to morphine.	Possesses an antitussive effect.	
Elimination	Excreted in 4-6 15-60% excreted as glucuronide daily 5-6 days	Completely detoxified in body	Partly detoxified by liver and partly eliminated unchanged.	Antagonized by naloxone.
Tolerance and addiction	Similar to morphine. Tolerance develops as rapidly. Under Harvard Narcotic Law	Tolerance develops. Addiction liability less than morphine. Under Harvard Narcotic Law	Tolerance develops after repeated doses. Addiction liability equivalent to morphine. Suppression morphine withdrawal completely. Morphine does not. Does equivalent to morphine studies addition.	Appears to have addiction quality but less than morphine.
Preparation	6 mg. tablets or 2 mg. per cc. for I.M. use. Dose 8-12 mg.	60-80 mg. I.M. May be used shortly L.V. Not used orally	60-80 mg. I.M. Effective orally 30-70 mg. Duration 5-6 hrs.	Base 70 or 1.0 mg./cc. Dose 3 to 6 mg. I.M. Dose 1 to 2.0 mg. L.V.

# ANTINARCOTICS—N-ALORPHINE (NALLINE)

**HISTORY**—Synthesis and pharmacologic actions first described in 1942 by Weijlard and Erickson. Hiller (1943) and also Unna noted that the compound antagonized the action of morphine in animals. Hart and McCauley (1944) reported additional studies confirming Unna's findings. Huggins and co-workers (1950) and Smith, and Lehman reported experimental studies in man. Possibility that an antidote might be found first indicated by Pohl (1914) who noted that N-allyl-nor-codeme antagonized morphine.

**DESCRIPTION**—Chemical name is N-allyl-normorphine. Nalorphine is a congener of morphine. A methyl group on the nitrogen atom is replaced by an allyl group. The drug is not a stimulant or convulsant. It is a narcotic far more feeble than morphine.

**Central**—Used alone exhibits a mild hypnotic effect. Does not restore consciousness. Definite depression of respiration, dyspnea and hallucinations. E.E.G. Does not restore to awake patterns. May even slow waves.

**Analgesic Action**—Alone has analgesic potency equal to or nearly equal to morphine. Not satisfactory for pain relief due to side actions.

**State of Consciousness**—Patients become more responsive to external stimuli. Anesthetizing does not occur (except in adults).

**Eye**—Causes constriction of the pupil. Used in combination with morphine in overdose it relaxes pupil.

**Cough Center**—Exerts an anti-tussive effect equal to codeine. Not used for this purpose. Exerts an additive effect with that of morphine and codeine.

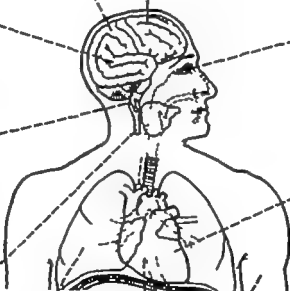
**Heart**—No circulatory effects observed.

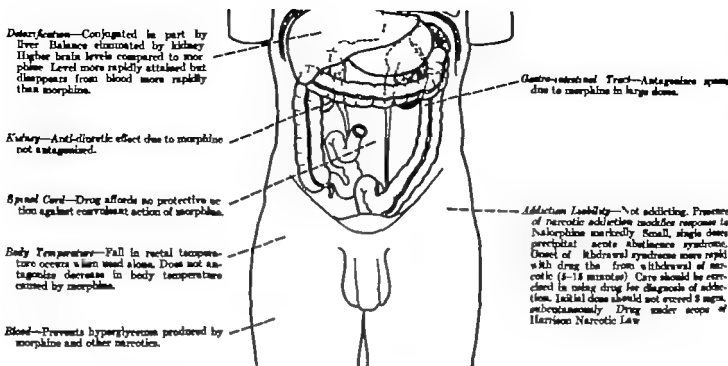
**Respiratory Center**—Sensitivity to carbon dioxide restored after depression due to morphine.

**Blood Pressure**—No significant changes. Restores blood pressure reduced to normal state.

**Lungs**—Minute volume exchange increased an average of 35% in narcotic depressed patient. Mild depression if used alone. Restores response of respiratory center to CO<sub>2</sub> when depressed by morphine.

**Pulse Rate**—Slight but significant slowing in cardiac rate.





**Onset and Duration of Action**—Usually with 5-8 minutes, less than 15 minutes. Response lasts from 1½ to 4 hours. Does not antagonize and respiratory depression. May even enhance it. Injected into umbilical vein antagonizes respiratory depression in asphyxiated babies born of mothers treated with narcotics. Pre-treatment of severely depressed mother before birth prevents or decreases asphyxia of newborn.

**Combination with Narcotics**—(10 mgm. morphine, 3 mgm. Nalorphine). Gave depressant effects equal to 15 mgm. morphine. Indistinguishable from morphine alone. Response to CO<sub>2</sub> and minute volume same.

**Dosage**—3 mgm. intravenously repeated after 4-5 minutes until 15 mgm. are administered. Failure to obtain some response with 15 mgm. is presumptive evidence depression is due to non-narcotic substances. Doses exceeding 15 mgm. ordinarily not necessary. 0.1 to 0.5 mgm. by umbilical vein for newborn. 0.75-1 mgm. per 10 lbs. body weight for children.

**Antagonism to Other Drugs**—Does not antagonize thiopental, barbiturates and other barbiturates or hypnotic of non-barbiturate type or the volatile anesthetics.

**Preparation**—Acc. ampules containing 5 mgm. per cubic centimeter.

## LEVALLORPHAN

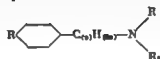
**DESCRIPTION**—Levallorphan is N-allyl-dromoran. It is a counterpart of dromoran with the methyl group replaced by an allyl group. It is approximately 3 to 5 times more potent than Nalorphine. It exerts the same pharmacologic effects. Does not come under the scope of the Harrison Narcotic Law.

**DOSE**—Adults 2 mgm. is equivalent to 5 mgm. of Nalorphine. For infants 1/10 to 1/5 mgm. is usual dose.

## SECTION XI LOCAL ANESTHETICS

### LOCAL ANESTHETICS

Local anesthetics (cocaine and other alkaloids derived from coca plant excepted) are synthetic aromatic or heterocyclic compounds. Two large groups may be differentiated: one composed of non-nitrogen containing alcohols, the other composed entirely of nitrogenous compounds. These conform to a general structure composed of a primary, secondary or tertiary amine and an aromatic nucleus (usually an acid) separated by an intervening side chain thus:



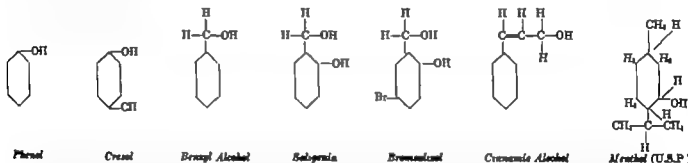
Radicals may be substituted on various positions of the aromatic nucleus. The amine may be primary, secondary or tertiary. The alcohols are suitable for topical use and are non-injectable. They exert their action by virtue of being protoplasmic irritants.

The injectable local anesthetics are nitrogenous derivatives and of the type I, the second group. The majority of this group are esters. A few are amides and other miscellaneous types. Their classification chemically is as follows:

Local anesthetics  $\left\{ \begin{array}{l} \text{alcohol-phenol, novethol, benzyl alcohol, etc.} \\ \text{nitrogenous bases} \left\{ \begin{array}{l} \text{esters-cocaine, procaine, metycaine, etc.} \\ \text{miscellaneous group-nupercaine, holocaine, quinize} \end{array} \right. \end{array} \right.$

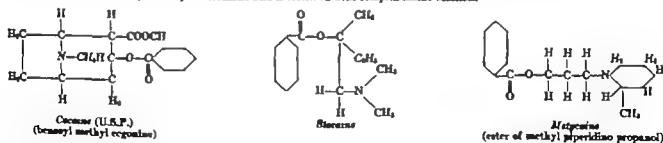
Physical agents such as cold, pressure, electricity induce local anesthesia, but are limited in clinical usefulness.

**Alcohol Group**—Both aromatic aliphatic and heterocyclic alcohols comprise this group. Aliphatic alcohols are of little importance as local anesthetics. They are liquids, contain no nitrogen, are neutral or acid in nature, moderately soluble in water. Benzyl alcohol is the most widely used. The following alcohols belong in this group:

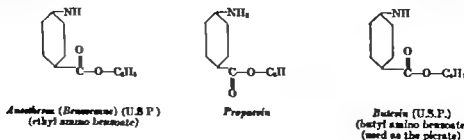


**Ester Group**—This group is the largest, the most important, and includes most of the drugs in current use. Structurally each is composed of an acid and an alcohol, upon which is one or more nitrogen atoms usually in the form of a tertiary amine. The amine may be on the alcohol portion, the acid portion or both. The acid is usually aromatic in nature. Esters are basic, form water-soluble salts with acids. Esters may be classified according to the acid from which they are formed.

**Aromatic Acid Esters**—Benzoic acid, the simplest aromatic acid is esterified with complex amino alcohols.



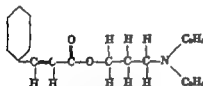
**Pure-aromatic Benzoic Acid Esters**—1. Slightly soluble type. Formed from simple aliphatic alcohols. Possess low toxicity. Useful for surface anesthesia only.



E. Soluble type (very important group) Formed from complex amine aliphatic alcohols.

	Amino Group	Acid	Alcohol	Amino Group
Procaine	-H	-CH <sub>2</sub> -CH	-C <sub>6</sub> H <sub>4</sub>	-C <sub>6</sub> H <sub>4</sub>
Betyn	-H	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub>	-C <sub>6</sub> H	-C <sub>6</sub> H <sub>2</sub>
Propocaine	-C <sub>6</sub> H	-CH <sub>2</sub> -CH	-CH <sub>3</sub>	-CH <sub>3</sub>
Larocaine	-H		-C <sub>6</sub> H <sub>4</sub>	-C <sub>6</sub> H <sub>4</sub>
Tutocaine	-H		-CH <sub>3</sub>	-CH <sub>3</sub>
Isocaine	-H	-CH <sub>2</sub> -CH <sub>3</sub>	-C <sub>6</sub> H (Iso)	-C <sub>6</sub> H (Iso)
Monoocaine	-H	-CH <sub>2</sub> -CH	-C <sub>6</sub> H (Iso)	-H
Azylocaine	-H	-CH <sub>2</sub> -CH <sub>3</sub>	-C <sub>6</sub> H <sub>11</sub>	-H

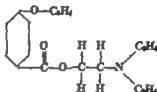
Cocaine Acid Esters—



Apithesine (N,N R.)  
(diethylsuccinate propyl ester)

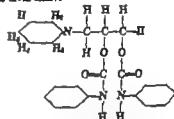
Ortho Amino Benzoic Acid Esters—

Pure Ethoxy Benzoic Acid Esters—

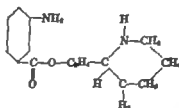


Isutocaine  
(diethylamine ethanol ester)

Carbamate Acid Esters—



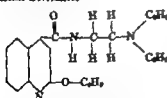
Diathesine (N,N R.)  
(piperidine propionic diethyl urethane)



Loxaine

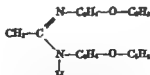
Miscellaneous Group—Drugs in this group are compound products, not esters.

Quinoline Derivatives—



Nupercaine (N,N R.)  
(diethyl oxy-chlorosuccinate acid—diethyl di-ethylene diamide)

Pure Ethoxy Aniline Derivatives—



Helocaine (U.S.P.)  
Phenocaine (U.S.P.)  
(ethoxy diethoxy-diphenyl aniline)

Quinine Derivatives—

Example, most important, is locaine, isomer of hydroquinone (capable of prolonged anesthesia)

**PROPERTIES**—The nitrogenous local anesthetics are basic, bitter compounds. Many are powders, some are oily liquids. Local anesthetics are prepared as salts of hydrochloric, sulfuric and other acids. The acid used to form the salt is selected from the standpoint of solubility. Salts are crystalline, water soluble, and acid in reaction. Alkaline precipitates the free base from aqueous solutions of the salt. Bases are more soluble in oils and organic solvents than in water. They will reform salts from acids. Bases are less stable than the salts. Local anesthetics respond to many reactions of alcohols and yield precipitates with alkaloidal reagents and salts of heavy metals, such as mercury and silver. Many local anesthetics decompose upon heating, by the action of light, air, acids, and other agents. Salts of local anesthetics hydrolyze to a variable extent in aqueous solutions, depending upon the structure of the molecule and the acid forming the salt.

## BIOLOGICAL EFFECTS OF LOCAL ANESTHETICS

Local anesthetics in sufficient concentrations (1) affect all cells (2) have a special predilection for nerve tissue (3) have a reversibility of action. They exert their effect by blocking conduction when applied at any single point in a neuron.

**Colloids**—Ultra microscopic flocculation of protein occurs. Action is reversible. Cell function restored to normal after removal of drug.

**Lipids**—Free base more soluble in lipoids than water. Affinity for and effect on nerve tissue may be partly due to lipid solubility.

**Ions**—Potassium ions diffuse from within outward and concentrate on cell surface.

**Metabolism**—Oxygen consumption reduced. Carbon dioxide output decreased. Azotemia output reduced.

**Electrical Phenomenon**—Drug interferes with ability of nerve to become depolarized as action potential traverses nerve fibre. A blockade of nerve impulses occurs as potential arrives at site of application of drug on fibre.

**Permeability of Cell Membrane**—Usually decreased. Unionized molecules of salt diffuse into cell.

**Adsorption**—Base and ions of salt are adsorbed to negatively charged particles in vitro. Similar response may occur in vivo.

**Surface Tension**—Lowered in vitro by many drugs. Similar effects may occur in vivo lowering interfacial tension in colloid systems.

**Osmosis**—Hypertonic and hypotonic solutions alter osmotic pressure if injected in tissues and cause irritation or swelling of cells.

## FACTORS INFLUENCING DURATION AND INTENSITY OF BLOCKADE BY LOCAL ANESTHETICS

**Site of Application**—Blockade occurs at site of application only. Effective only here in the neuron, along portion of the axon, dendrite or cell body.

**Configuration of Molecule**—Potency and duration depend directly upon ease of diffusion into nerve tissues. Diffusion depends upon physical properties induced by molecular configuration.

**Concentration**—Latent period is time interval between moment of application and establishment of blockade (Shortened as concentration increases.) Interval greater with longer lasting drugs. Concentration increases duration up to a point beyond which it is little affected.

**Temperature**—Onset of action hastened by increase in temperature of injected solution.

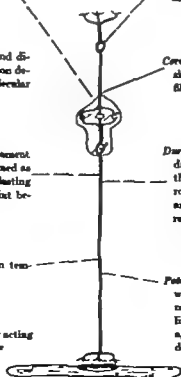
**Elimination**—More rapidly detoxified drugs are shorter acting due to rapid decrease of concentration in nerve tissue.

**Fibre Size**—Smaller fibres (sensory and autonomic) affected before large (motor). Selectivity is a function of fibre size and not due to chemical composition of nerve.

**Covering**—Penetration more rapid into unmyelinated unsheathed fibres; action potential disappears first. Myelinated fibres without sheaths affected before those with sheaths.

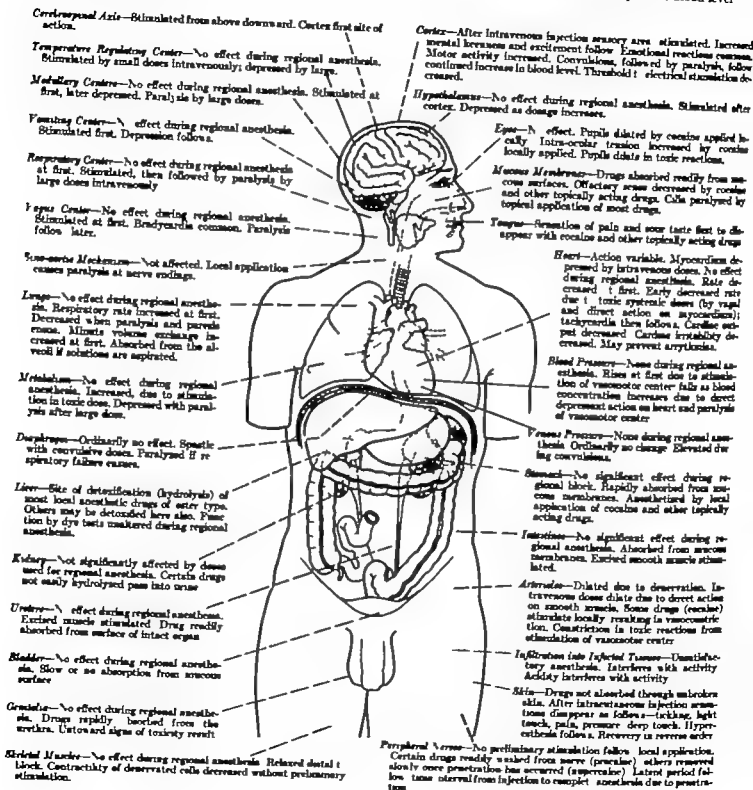
**Duration of Contact**—Depends upon the ease of elimination of drug from site of application. The more rapid the removal the shorter the duration. Influenced by vascularity surrounding site of injection. Longer contact allows penetration and sustained concentration in nerves. Epinephrine inhibits removal.

**Potentiating Agents**—Non-anesthetic drugs enhance action when combined with the agent. Permeants (caffeine, theobromine, etc.) dyes (methylene blue) proteins (albumin, globulin, glutone, etc.) ions (potassium, calcium) alkalinizing agents (bicarbonates, carbonates), are effective to various degrees.



## GENERAL SYSTEMIC EFFECTS OF LOCAL ANESTHETICS

Local anesthetics are absorbed from site of injection and carried to liver, kidney and muscles in blood. Circulating drug gives rise to certain systemic responses, the nature and intensity of which depend upon the blood level of the drug.



## TOXICITY OF LOCAL ANESTHETICS

Two types of toxicity to local anesthetic drugs are recognized (1) Local toxicity—direct damage to tissues at the site of application, (2) systemic toxicity—caused by the drug circulating in the plasma. Ultimately all of a local anesthetic passes from the site of injection or topical application into the blood. Rapid absorption results in high plasma levels and syndromes of systemic toxicity.

## FACTORS INFLUENCING LOCAL TOXICITY

1. Inherent nature of drug. All local anesthetics are protoplasmic poisons capable of causing death of tissue by dehydration or chemical alteration of cellular proteins if used to excess.
2. Solubility of drug. Certain drugs precipitate at pH of tissues. Precipitate acts as foreign body.
3. Concentration of drug. Concentrated solution of normally non-injurious drug at 1 cm<sup>2</sup> causes local damage.

## TYPES OF SYSTEMIC TOXICITY

1. Intolerance
  - (1) Intolerance—Normal quantities result in symptoms of over dosage.
  - (2) Overdosage—Use of excess quantities.
2. Allergic
  - (1) Anaphylaxis—Sudden circulatory collapse.
  - (2) Antigen antibody type—Eczema, urticaria, bronchospasm, laryngeal edema.
3. Idiosyncrasy—Response not ordinarily expected or characteristic of the drug.

## FACTORS INFLUENCING SYSTEMIC TOXICITY

1. Potency of drug. An increase in potency of 1 drug does not necessarily parallel increase in toxicity. Dosage must be scaled in proportion to potency of reference drug (Tetracaine 1 mgm. = procaine 10 mgm.)
2. Concentration of drug. Concentrated solutions absorbed more rapidly than dilute from site of application. Least concentrated effective solution should be employed.
3. Vascularity of tissue. Rapidity of absorption increases with degree of vascularity. Vasoconstrictors inhibit absorption in highly vascular areas. Sympathomimetics promote spreading and facilitates absorption.
4. Blood level. Varies with rate of absorption from given site, vascularity and total dose. Rapid increase to a plasma level induces convulsions.
5. Rate of elimination or detoxification. Rapidly and more easily detoxified drugs are safer.

## TYPES AND SYSTEMS OF SYSTEMIC REACTIONS

Systemic vulnerable to high plasma levels

1. Central Nervous System
  - (a) Causes stimulation (characterized by excitement, delirium, nausea, vomiting, convulsions). This is followed by paralysis (coma, respiratory failure) if dose is large.
  - (b) Causes depression—about stimulation (characterized by coma).
2. Cardiovascular System
  - (1) Causes myocardial depression (hypotension, bradycardia).
  - (b) Causes vasodilatation from smooth muscle depression or vaso-motor center depression (characterized by hypotension, brady-cardia).
  - (c) Combination of a and b.
3. Combined Vascular and Central Nervous System (1 & 2)

## METHOD OF TESTING SYSTEMIC TOXICITY

1. Intravenous injection. Drug injected rapidly at a constant rate into animals until convulsions occur. Procaine drug of reference. Absolute toxicity—milligrams causing convulsions divided by milligrams procaine producing same effect in same time under identical conditions.
2. Intraperitoneal injection. An index of rate of absorption and effects produced by single dose.
3. Subcutaneous injection. An index of diffusibility. Permits study of varying concentration and effect of vascularity on absorption.

## TREATMENT OF SYSTEMIC TOXIC REACTIONS

1. For prophylaxis. Prevention is better than cure. Systemic reactions from local anesthetics are lethal. In order to avoid reactions:
  - (1) use least amount of drug necessary to produce blockade
  - (2) use a eulaxation solution possible.
  - (c) attempt aspiration while injecting drug to rule out placement in vessel
  - (d) use vasoconstrictors to retard absorption.
  - (e) use short-acting barbiturates (sodium barbital 100 mgm.) for pre-medication one hour prior to injection of drug
2. For convulsions. Barbiturates IV. Ultra short-acting barbiturates (thiopental, thiopental, etc.) most effective. Short-acting second best. Long-acting suitable in absence of short-acting.
3. For respiratory failure. Artificial respiration. Analgesics of no benefit.
4. For circulatory collapse. Restore blood pressure with sympathomimetic amines (ephedrine, phenylephrine (neosynephrine) or methoxamine (Vasostyl).
5. For cardiac arrest (Asystole)—cardiac massage

## CHARACTERISTICS OF ALLERGIC RESPONSES

1. Antigen-antibody type. Cutaneous manifestations wheezing, urticaria, eczema, bronchospasm occur after repeated exposure to drug. Cross sensitization possible (e.g. procaine, benzocaine) Use anti-histamines.
2. Anaphylactoid. Sudden circulatory collapse after injection or application of infinitesimal quantity of drug. No previous exposure. Probably due to histamine release. Treat for circulatory collapse and respiratory failure.

## CHARACTERISTICS OF INTOLERANCE

1. Less than accepted quantity of drug produces signs of overdosage occurs in aged debilitated patients. Treatment as for overdosage.

## CHARACTERISTICS OF IDIOSYNCRASY

1. Normal response not ordinarily expected of drug—such as tachycardia, hypertension, hallucinations, etc. Treatment symptomatic.



## ABSORPTION AND SYSTEMIC TOXICITY

**Subcutaneous Tissue (Scalp)**—Highly vascular. Absorbed rapidly. Anesthesia of brief duration unless vasoconstrictors are added to retard absorption.

Barbiturates do not influence rate of absorption.

**Subcutaneous Tissue**—(Average vascularity) Absorbed gradually. Level curves barely detectable. Peak reached in 10-30 minutes. Vasoconstrictors retard absorption. Epinephrine 1:100,000 most effective agent. Nor-epinephrine effective, but may cause spasm from intense vasoconstriction. Hyaluronidase promotes spreading. Increases blood level.

**Skin**—N absorption from unbroken skin. Absorbed from broken skin surface from aqueous solutions, suspensions of true base or water soluble esters. No absorption when applied to 1st and 2nd degree burns. Absorbed from broken blisters of 3rd degree.

**Scars Surface**—Rapidly absorbed from peritoneal and pleural surfaces. Blood levels comparable to those of rapid intravenous injection follow intraperitoneal injection.

**Bone Marrow**—Similar to intravenous injection. Rapid rise in plasma level.

**Intra-arterial**—Drug passes into and partially stored in tissue. Application of tourniquets to an extremity prevent passage of drug into venous circulation. Regional anesthesia of extremity results.

**Intravenous**—Plasma level proportional to rate of injection of given dose. Barely detectable levels follow slow infusion (1% procaine—1 gpc per hour). Rapid injection results in abrupt rise and steep plasma levels "arrest reactions".

**Spinal Canal**—Passage into blood slower than from other areas of body. Blood levels seldom detectable following doses used for spinal anesthesia. Vasoconstrictors retard absorption and increase duration 80% or more. 1 order of decreasing effectiveness are: epinephrine, norepinephrine, pituitrine, phenylephrine (moxiphetine). Epinephrine, orethyl, methoxamine ineffective. Systemic prompt responses uncommon following intrathecal injection of solutions.

**Peridural Space**—Drug diffuses along nerves through intravertebral foramina. Absorption curves follow similar patterns to subcutaneous. Vasoconstrictors retard absorption.

**Cerebral Tissue**—Drug absorbed from venous sinuses.

**Lymphatic**—Part of drug passes from tissue spaces into lymph and thence into venous system after infiltration.

**Eye**—Absorbed through conjunctival membranes from aqueous solutions. Blood levels not detectable. Conjunctival injection follows use of hypertonic solutions or in allergic states.

**Pharynx**—Rapidly absorbed through mucous membranes from aqueous solutions of salts, suspensions of base or water soluble esters. Plasma level curves comparable to those of slow (8 ml) IV injection. Absorption depends upon total weight applied to a given area and not concentration. 1 cc. 4% yields same type curve as 8 cc. 8%. Vasoconstrictors do not retard absorption from mucous membranes. Drying agents (atropine) do not retard absorption.

**Trachea and Bronchi**—Absorption similar to but more rapid than from pharynx. Peak levels high and more quickly attained.

**Alveoli**—Hydrostatic forces designed to draw fluids from alveoli into capillaries to maintain "dry lung." Rapid absorption follows ventilation or inhalation of neutralized solutions.

**Esophagus**—Poorly absorbed from this site. Barely detectable blood levels result.

**Stomach**—Plasma levels low. Drugs probably hydrolyzed in passage through liver from portal system.

**Rectum**—Absorbed from mucosa of anal canal.

**Urethra**—Significant blood levels. Amount of absorption increases if membrane is traversed from instrumentation.

**Bladder**—Not absorbed from this site.

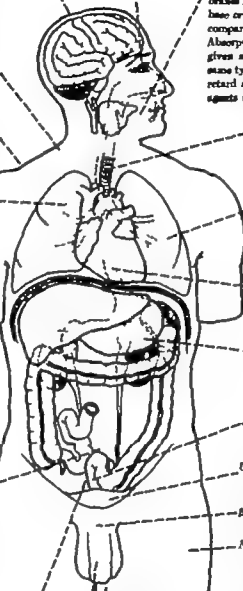
**Nerve**—Drug penetrates into axons dendrites or cell body. Hydrocarbon pole (lipophilic) orients itself into lipid phase. Amino group (hydrophilic) orients into aqueous phase.

Gradient established from tissue fluid into axons by deposition of drug peripherally.

Drug enters axonal membrane (at node of Ranvier only in myelinated fibers). Stabilizes membrane. K and Na unable to migrate in or out. Depolarization and repolarization necessary for propagation of action current to transmit nerve impulse does not occur.

## RECOVERY:

Peri-anaxial concentration of anesthetic declines as drug passes into lymph. Gradient reversed; drug passes from axons to lymph. Permeability and function restored.



	Procaine (U.S.P.)	Pontocaine	Tutocaine	Larocaine
Synonyms	Ethocaine Pianocaine Necaine Nervocaine Allocaïne Scirocaine	Pentocaine (N.N.R.) Tetracaine (U.S.P.) Amethocaine Pantocaine	Butaina.	
Chemical nature	Para amino benzoic acid ester of diethyl amino ethanol.	Para butyl amino benzoic acid ester of dimethyl amino ethanol.	Para amino benzoic acid ester of dimethyl amino methyl butanol.	Para amino benzoic acid ester of $\beta$ dimethyl, $\beta$ diethyl propanol.
Properties	Base—white colorless, bitter powder M.P. 80 to 81° Sol. in $H_2O$ . Soluble alcohol chloroform. Hydrochloride M.P. 123 to 124° One gm. dissolves in 8 cc. $H_2O$ Solution has pH 6.0.	Base—white, colorless, bitter powder Sol. in $H_2O$ Hydrochloride M.P. 144 to 145°C. Sol. 1 in 7 $H_2O$ at 25°C Easily precipitated by weak bases and car bonates.	Hydrochloride Light ivory colored, odorless, bitter powder M.P. 216 to 215° Sol. 1 in 4 $H_2O$	Hydrochloride White powder M.P. 196 to 197° Sol. 1 in 8 $H_2O$ and 10 alcohol.
Prepared by	Elkhorn 1903.	Elab 1933.	Shulermann 1923.	Mannich 1930.
Potency	Procaine is standard for comparison of other local anesthetic drugs.	Approximately 10 times greater than procaine in man.	Some has greater than procaine Topically two to four times greater than cocaine	Approximately four times greater than procaine
Toxicity	Not known for man. Administered intravenously over one hour One gram easily tolerated.	Relative toxicity equals procaine. Absolute toxicity approximately 10 times greater than procaine	Two to four times greater than procaine	Two and one half times greater than procaine
Detoxification	Hydrolyzed in liver to para amino benzoic acid and diethyl amino ethanol. Hydrolyzed by an enzyme in blood.	Hydrolyzed in liver	Probably in liver	Presumably in liver by hydrolysis.
Stability of solutions	Stable May be boiled repeatedly and autoclaved.	Stable May be boiled repeatedly and autoclaved	Stable if boiled for a few minutes.	Stable Sterilized by boiling for 10 min.
Onset of action	Immediate—two to five minutes.	Five to 10 minutes.	Immediate by injection. Two to three minutes topically	Immediate.
Duration	Averages one hour	Averages two hours.	One to two hours.	Three hours.
Dose: Intradermally low medium high Profound Infiltration Nerve Block Topical Conjunctival Oil solution	80 to 100 mg. 100 to 150 mg 150 to 300 mg 75 to 1.0 gm. (5%) 1 gm. (1%) 1 gm. (5%) Not effective Not effective 5%	5 to 15 mgm. 7½ to 15 mgm 16 to 30 mgm. 15 mgm. 0.1%. 15 mg. 0.1%. 5%.	Not used intraspinally  0.5% solution	Not used intraspinally Infiltration .25%. Eye 1 to 5%. Mucous membranes. 1 to 10%.
Remarks	Least toxic and most widely used local anesthetic drug. Compatible with epinephrine	Circulatory type of toxic response more common than convulsive reaction. Compatible with epinephrine	Possesses topical activity. Little used clinically Compatible with epinephrine	Possesses 2.5 the surface activity of cocaine Compatible with epinephrine No mydriasis.

	Pantethine	Butyn	Monocaine	Benzocaine	Propen
Synonyms		Eutacaine (U.S.P.)	Eutecamine	Anesthesin, Americaine	
Chemical nature	Menthane sulphomate <i>m</i> -diethyl isocinnel ester of para amino benzoic acid.	Para amino benzoic acid ester of di-butyl amino propanol.	Para amino benzoic acid ester of mono-isobutyl amino ethanol.	Para amino benzoic acid ester of ethyl alcohol.	Para amino benzoic acid ester of propyl alcohol.
Properties	Hydrochloride. White or slightly yellow powder M.P. 157 to 158°C. Soluble 1 in 3H <sub>2</sub> O. pH 6.8.	Sulphate. White odorless powder. Melts 80 to 100°C. Soluble 1 in 11H <sub>2</sub> O. Soluble in alcohol.	Hydrochloride. Soluble white powder with bitter taste. Formet more soluble than hydrochloride. Used for spinal anesthesia.	Base: white, odorless, tasteless powder. One gm. dissolves in 2.5 l. H <sub>2</sub> O, 5 cc. alcohol, 30 cc. almond oil. Soluble in hydrochloric acid.	White odorless, tasteless powder M.P. 73°C. Solubility approximately same as benzocaine.
Prepared by	Karrer 1941	Ramm and Volander 1918.	Goldberg 1934.		
Potency	Ten times greater than procaine	Surface anesthetic potency approximates cocaine	One and one-half times more potent than cocaine	Very low potency due to insolubility in water	Low potency due to insolubility in water
Toxicity	Two to three times greater than procaine	Three times greater than procaine	Approximately as toxic as procaine	Relatively non-toxic due to low water solubility	Relatively non-toxic due to water insolubility
Detoxification	Probably in liver	Probably in liver	Presumably hydrolyzed in liver	Hydrolyzed by liver	Probably by liver.
Stability of solutions	Stable	Stable. Solutions sterilized by boiling	Stable. May be bottled or autoclaved.	Stable in aqueous alcoholic and oily solutions.	Stable in aqueous and oily solutions and esters.
Onset of action	Immediate	Immediate.	Immediate	Immediate.	Immediate.
Duration		Approximately one hour	1 to 1½ hours.	As long as it remains in contact.	As long as it remains in contact.
Dose: Intrathoracically low medium high Peribulbar Infiltration Nerve Block Topical Ointment Oil solution	5 cc. 0.5% (50 mgm.)  0.15 to 2% 2%   2%	Not used Not used. Not used   2% for eye. 2% for eye	40 to 80 mg 80 to 100 mgm. 100 to 150 mgm. 1% ½ to 1%	Not used. Not used. Not used. Not used. Not used.  3% dusting powder 50% ointment (Americaine)	Not used. Not used. Not used. Not used. Not used.  2 to 20% ointment.
Remarks	Not used in clinical practice	Used primarily as topical anesthetic	Offers little more procaine than procaine. Has some vasoconstrictor action.	Reliable only as a topical anesthetic. Added to oil solutions for securing prolonged effect.	Reliable only as topical anesthetic.

	Buteisa	Orthoform (old)	Orthoform (new)	Locaine	Cocaine
Synonyms			Orthocaine.	PT 10 Peridocaine	
Chemical nature	Para amino benzoic acid ester of propanol.	Methyl ester of 3-hydroxy 4-amino benzoic acid.	Methyl ester of 3-amino 4-hydroxy benzoic acid.	Piperidyl propanol ester of orthoamine benzoic acid.	Benzoic acid ester of methyl ergonine
Properties	Insoluble white powder melting at 34 to 37°C. Forms yellow salt with picric acid.	White powder Melts at 120-140° Forms hydrochloride Not very soluble in water Salts are more soluble	White odorless, tasteless powder Melts at 141 to 145° Insoluble in water Forms hydrochloride Melts at 180°C. Soluble in water 1:10.	White bitter powder Forms hydrochloride Melts at 208°C. Forms a 2% solution.	Colorless, crystalline, white powder Forms hydrochloride which melts at 123°C. One gram dissolves in 0.4 cc water White powder from coca leaves. Isolated by Goedicke in 1853
Prepared by					Prepared by Niemann in 1800 Carl Koller in 1884 discovered its value for local anesthesia.
Potency	Paraldehyde benzocaine	Paraldehyde benzocaine.	More potent than benzocaine.	Approximately same as procaine.	Approximately two to three times more potent than procaine.
Toxicity	Low by virtue of poor solubility	Low May be used internally	Low	Approximately same as procaine	Approximately four times more toxic subcutaneously than procaine
Detoxification	Hydrolyzed by liver (?)	Hydrolyzed by liver	In the liver by hydrolysis (?)	Liver?	Approximately 80% hydrolyzed by liver to benzoic acid and ergonine Best eliminated unchanged.
Stability of solution	Of mixtures and solutions stable	Stable.	Stable.	Stable	Not heat stable Decomposed by boiling and upon standing.
Onset of action	Immediate.	Immediate	Immediate	Immediate.	Immediate.
Duration	As long as in contact with tissues.	As long as in contact with tissues.	As long as in contact with tissues.	Averages 45 minutes.	Averages one hour
Dose	Buteisa picrate ointment 1%.	Same as orthoform.	Powder with starch 10-20%. Ointment 10-20%.	20 to 40 mgm. for spinal anesthesia.	2 to 4% topically Not recommended for infiltration, nerve block or spinal anesthesia. Is standard of comparison for drugs used topically
Remarks	Used as a surface anesthetic entirely	Same structure as orthoform (new) except position of amino and hydroxyl reversed. Not used clinically	May cause necrosis and inflammation on raw surfaces. Little used clinically	Motor effects minimal. Provides mostly sensory anesthesia.	Possesses mydriatic action, local vasoconstrictor action, addiction properties, generalized vasoconstrictor action. Under Harrison Narcotic Law

	Meperidine	Allylpin	Intracaine	Apothecaine	Nupercaine
Synonyms	Nerolind, Papercaine.	Amidocaine	Duthocin, Markaine.		Procaine (B.K.) Dibucaine.
Chemical nature	Benzole acid ester of methyl piperidyl propanol.	Benzole acid ester of tetra methyl diamine ethyl propanol.	Pure ethoxy benzole acid ester of diethyl amine ethanol.	Cinnamic acid ester of diethyl amino propanol.	Beta diethyl amine ethyl anilide of butyrosyric-cholic acid.
Properties	White powder. Forms hydrochloride. Melts at 172 to 175°C. Soluble 1 in 111/2.	White powder. Soluble in water and alcohol. Forms hydrochloride which melts at 170°C.	White powder. Soluble in water. Forms hydrochloride.	Hydrochloride is a white powder melting at 126°C. Soluble in water and alcohol. Free base occurs as an oil.	Hydrochloride is white powder which melts at 97°C. Very soluble in water. pH 6 base easily precipitates.
Prepared by	McElwain 1930	1906 by Hoffman.			Meischer 1903
Potency	Approximately 1 1/2 times more potent than procaine.	Four to five times more potent than procaine.	Approximately 1 1/2 times more potent than procaine.	Approximately that of procaine.	Approximately 18 times that of procaine.
Toxicity	Slightly greater than procaine.	Two times greater than procaine subcutaneously.	Approximately 1 1/2 times that of procaine.	Approximately twice as toxic as procaine.	Approximately 18 to 19 times greater than procaine.
Detoxification	Hydrolysed in the liver.	Hydrolysed in the liver.	Hydrolysed in the liver.	Hydrolysed in the liver.	Hydrolysed in the liver.
Stability of solution	Stable. May be boiled and autoclaved.	Not stable. Boiled at 100° Decomposes after 4 to 5 minutes.	Stable. Boilable for sterilization.	Stable and boilable.	Stable. May be boiled and autoclaved. Mixes with glucose.
Onset of action	Immediate.	Immediate.	Immediate.	Slower than procaine.	Onset in 10 seconds.
Duration	Lasts one hour.	Similar to cocaine.	Lasts over 1 1/2 hours.	Approximately same as procaine.	Lasts 2 1/2 to 3 hours.
Dose	Intrathecally low medium high Peridural Infiltration Nerve Block Topical Oral Oil solution	Used for topical anesthesia 0.5 to 1%. Approximates cocaine in potency as topical anesthetic.	Approximately 1/2 dose and concentration of procaine. Used for spinal and infiltration. Topical action slight.	1 1/2% for infiltration, 2 cc. of a 4% solution for spinal. 4% topical.	Infiltration 0.1%. Block 0.1%. Spinal 2 1/2 to 5 mgm. low 5 to 10 mgm. medium, 10 to 15 mgm. high. 1% elemental. Oil 5 mgm. per cc.
Remarks	Possesses half potency of cocaine topically. Does not interfere with action of sulphamides.	Compatible with epinephrine. Not used for injection.	Used as substitute for procaine. Has little to offer over procaine.	Used instead of procaine. Has little to offer over procaine.	Not derived from quinine. Most potent local anesthetic. Possesses some local toxicity. Causes slough when injected subcutaneously.

	Eucaine	Quinac	Procaine	Bromalol	Benzyl Alcohol	Xylocaine
Synonyms			Holocaine			Lidocaine
Chemical nature	An alkaloid-benzyl hydrocarbons. Related to quinine.	An alkaloid-methyl eucaine. Contains 1 nitrogen atom. Highly basic.	Not a ester. Built from phenethyl molecule.	4-Methoxy-2-hydroxy benzyl alcohol.	Phenyl carbinol, an aromatic alcohol.	<i>n</i> -diethylamino-2,6-dimethyl acetamide.
Properties	Forms dihydrochloride salt with nitrogen atom. White powder soluble 1 in 111 H <sub>2</sub> O at 18°C.	White, bitter powder forming salts with acids. Hydrochloride combined with urea most soluble preparation used for anesthesia.	Forms a hydrochloride-white powder. Melts at 160°. Soluble 1 in 90 H <sub>2</sub> O, also alcohol (U.S.P.)	White powder M.P. 107 to 108°C. Forms 1% solution in water. Soluble in alcohol, ether, oils, and glycol.	Colorless liquid with faint aromatic odor. Soluble 1 in 25 water. Boils at 80.5°C. Freely soluble in alcohol, ether, etc.	Base forms hydrochloride which is white powder stable and sterilizable.
Prepared by	Synthesized from quinine.	From cinchona bark.		Described by Mackl and Dunning.	Found in Jassin and Pers and Toti balsams.	Loftgren and Lundquist in 1943.
Potency	As those more potent than cocaine (typically Ten to twenty times more the procaine substantiveness).	Considerably greater than procaine.	Potency same as cocaine for topical use.	Low potency similar to benzocaine.	Low potency similar to benzocaine.	Approximately twice as potent and toxic as procaine. Possesses topical action.
Toxicity	Locally toxic. Low systemic toxicity. T is that of quinine.	Locally toxic. Produces slough. Excitation characteristic of procaine does not follow intravenous use.	Substantiveness toxicity twice that of cocaine. IV equals cocaine.	Non-toxic. Used orally as an antispasmodic. N convulsions intravenously.	Non-toxic. May be taken orally to relieve spasms.	Same systemic effects as procaine. Tends to produce drowsiness and anesthesia. Rapid absorption causes convulsion.
Detoxification	Detoxified in liver. All of an IV dose eliminated in 24 hrs.	Liver.	Destroyed in liver and eliminated slowly.	Liver?	Liver?	Liver slowly hydrolyzed.
Stability of solution	Stable in oil and water. Germicidal, boilable and can be autoclaved.	Stable in oil and water solution.	Stable.	Boilable. Self-sterilizing.	Boilable and stable.	Stable and boilable. Not an ester I am amide.
Onset of action	Slow. Causes burning.	Slow onset.	Similar to cocaine.	Slowly.	In several minutes.	Immediate. Diffuses rapidly into tissue.
Duration	Several hours. Onset action 10 hours to weeks.	Several days to weeks.	Similar to cocaine.	10 days to weeks.	Many hours when used in combination with procaine.	1 1/2 hours without epinephrine when infiltrated. 2 hours with epinephrine.
Dose	Axonal—not used. Infiltration 0.1% to 1%. 0.5% in oil 1-3 cc. at each injection site. Open wound 0.5 to 1.0%.	Rarely used. 0.5% in injection site.	1% for topical use in eye.	1% infiltration. 0.5% in peanut oil. 0.5% in propylene glycol.	1 to 4% topically or infiltration. Not recommended for infiltration.	1 to 2% solution for infiltration up to 4% topically. Maximum 1/2 gram.
Remarks	May cause slough. Used in combination with procaine to obtain prompt anesthesia.	Causes slough. Precipitates in tissues. Poorly soluble.	Action preceded by smarting and erythema.	N salt forms due to OH, but OH needed for activity. Some local tissue irritation occurs.	Local irritation. Usually combined with procaine, benzocaine, etc. for prolonged use.	Not irritating to tissues.

	Metycaine	Alypin	Intracaine	Apothecline	Nupercaine
Synonyms	Neotlarin. Piprocaine.	Amidricaine	Diethorin. Maxidain.		Perocaine (Brit.) Dibacaine
Chemical nature	Benzoic acid ester of methyl piperidyl propyl amol.	Benzoic acid ester of tetra methyl diamine ethyl propanol.	Para ethoxy benzoic acid ester of diethyl amino ethanol.	Chlornic acid ester of diethyl amino propanol.	Beta diethyl amino ethyl amide of butyrylcholinic acid.
Properties	White powder. Forms hydrochloride. Melts at 172 to 176°C. Soluble 1 in 11140.	White powder. Soluble in water and alcohol. Forms hydrochloride which melts at 170°C.	White powder. Soluble in water. Forms hydrochloride.	Hydrochloride is a white powder melting at 196°C. Soluble in water and alcohol. Free base occurs as an oil.	Hydrochloride is white powder which melts at 87°C. Very soluble in water. pH 8 base easily precipitates.
Prepared by	McElvain 1890.	1908 by Hoffman.			Meisner 1914.
Potency	Approximately 1½ times more potent than procaine.	Four to five times more potent than procaine.	Approximately 1½ times more potent than procaine.	Approximately that of procaine.	Approximately 1½ times that of procaine.
Toxicity	Slightly greater than procaine.	Ten times greater than procaine subcutaneously.	Approximately 1½ times that of procaine.	Approximately twice as toxic as procaine.	Approximately 10 to 15 times greater than procaine.
Detoxification	Hydrolyzed in the liver.	Hydrolyzed in the liver.	Hydrolyzed in the liver.	Hydrolyzed in the liver.	Hydrolyzed in the liver.
Stability of solution	Stable. May be boiled and autoclaved.	Not stable. Boiled at 100°C. Decomposes after 4 to 8 minutes.	Stable. Boils for sterilization.	Stable and heatable.	Stable. May be boiled or autoclaved. Mixes with glucose.
Onset of action	Immediate.	Immediate.	Immediate.	Slower than procaine.	Onset in 10 minutes.
Duration	Lasts one hour.	Similar to cocaine.	Lasts over 1½ hours.	Approximately same as procaine.	Lasts 2½ to 3 hours.
Dose	Intrathecal low medium high Peridural Infiltration Nerve Block Topically Ointment Oil solution	Used for topical anesthesia 0.5 to 4%. Approximate cocaine in potency as topical anesthetic.	Approximately ½ dose and concentration of procaine. Used for spinal and infiltration. Topical action slight.	1½% for infiltration 2 cc of 4% solution for spinal. 0% topical.	Infiltration 0.1%. Block 0.1%. Spinal. 2½ to 4 mgm. low 8 to 10 mgm. medium. 10 to 15 mgm. high. 1% ointment. Oil 2 mgm. per cc.
Remarks	Possesses half potency of cocaine topically. Does not interfere with action of sulphamonomide.	Compatible with epinephrine. Not used for injection.	Used as substitute for procaine. Has little to offer over procaine.	Used instead of procaine. Has little to offer over procaine.	Not derived from epinephrine. Most potent local anesthetic. Possesses some local toxicity. Causes although a less injected subcutaneously.

	Eucaine	Quinine	Phenacaine	Bromacaine	Benzyl Alcohol	Xylocaine
Synonyms			Holoraine.			Lidocaine
Chemical nature	An alkalioid-benzoyl hydroxypropine. Related to quinine.	An alkalioid-methyl caproate. Contains nitrogen atoms. Highly basic.	Not an ester. Built from phenethylin molecule.	2-Monobrom 2-hydroxy benzyl alcohol.	Phenyl carbinol, an aromatic alcohol.	$\alpha$ -diethylamino, 2,6-dimethyl acetamide.
Properties	Forms a dehydrate. Has two nitrogen atoms. White powder soluble 1 in 117 H <sub>2</sub> O at 15°C.	White, bitter powder forming salts with acids. Hydrochloride combined with urea most soluble preparation used for anesthesia.	Forms hydrochloride-white powder. Melts at 140°. Soluble 1 in 80 H <sub>2</sub> O, also alcohol (U.S.P.)	White powder M.P. 107 to 108°C. Forms 1% solution in water. Soluble in alcohol, ether oils, and glycol.	Colorless liquid with faint aromatic odor. Soluble 1 in 25 water. Boils at 60.5°C. Freely soluble in alcohol, ether etc.	Base forms hydrochloride which is white powder stable and sterilizable.
Prepared by	Synthesized from quinine.	From cinchona bark.		Described by Mack and Donaghy	Found in Jasmin and Persa and Tolu balsams.	Loftgren and Lundquist in 1943.
Potency	43 times more potent than cocaine topically. Ten to twenty times more the procaine substantively.	Considerably greater than procaine.	Potency same as cocaine for topical use.	Low potency similar to benzocaine.	Low potency similar to benzocaine.	Approximately twice as potent and toxic as procaine. Possesses topical action.
Toxicity	Locally toxic. Low systemic toxicity. Twice that of quinine.	Locally toxic. Produces enough. Excitation characteristic of procaine does not follow intravenous use.	Subcutaneous toxicity takes that of cocaine. IV equals cocaine.	Non-toxic. Used orally as an antispasmodic. N convulsions intravenously.	Non-toxic. May be taken orally to relieve spasms.	Same systemic effects as procaine. Tends to produce drowsiness and ammonia. Rapid absorption causes convulsion.
Detoxification	Detoxified in liver. All of an IV dose eliminated in 44 hrs.	Liver.	Destroyed in liver and eliminated slowly.	Liver?	Liver?	Liver slowly hydrolyzed.
Stability of solution	Stable in oil and water. Germicidal, boilable and can be autoclaved.	Stable in oil and water solution.	Stable.	Boilable. Self-sterilizing.	Boilable and stable.	Stable and boilable. Not an ester. Is an amide.
Onset of action	Slow. Causes burning.	Slow onset.	Similar to cocaine.	Slowly.	1 several minutes.	Immediate. Diffuses rapidly into tissue.
Duration	Several hours. Oil solution 10 hours to weeks.	Several days to weeks.	Similar to cocaine.	10 days to weeks.	Many hours when used in combination with procaine.	1 1/2 hours without epinephrine when infiltrated. 2 hours with epinephrine.
Dose	Spinal—not used. Infiltration 0.1%. Topical 0.5 to 1%. 0.5% in oil 1-6 cc at each injection site. Open wound 0.5 to 1.5%.	Rarely used. 0.6% causes enough at injection site.	1% for topical use in eye.	1% infiltration. 4% in peanut oil. 60% in propylene glycol.	1 to 4% topically or infiltration. Not recommended for infiltration.	1 to 4% solution for infiltration up to 4% topically. Maximum 1 gram.
Remarks	May cause enough. Used in combination with procaine to obtain prompt anesthesia.	Causes enough. Precipitates in tissues. Poorly soluble.	Action preceded by smarting and erythema.	N. alk. forms due to OH, but OH needed for activity. Some local tissue irritation occurs.	Local irritation. Usually combined with procaine, benzocaine, etc. for prolonged use.	Not irritating to tissues.



Name	Amide anes.	Ester anes.	Chlorprocaine	Hydroxyprocaine
Synonym	Amethone	Doracaine, Butoxyprocaine	Nomacaine	Oxyprocaine
Chemical structure	3 (beta diethyl amino ethyl 2, phenyl 4, benzo-furanone	3n butoxy diethyl amine ethanol ester of para- amino benzoic acid	Diethyl amino ester of 2, chlor 4, aminobenzoic acid	OH in position 2 in procaine
Properties	Topical anesthetic, anticholinergic	White, odorless crystalline powder butoxy benzoic acid.	White powder soluble in water	Similar to procaine.
Potency	Low potency	Similar to tetracaine.	Similar to procaine.	Similar to procaine. Onset more rapid, duration slightly longer
Toxicity	Used I.M. as spasmolytic. Not a convulsant.	Similar to tetracaine.	More rapidly hydrolyzed than procaine.	Slightly more toxic than procaine.
Detoxification		By hydrolysis.	By hydrolysis, aided by liver and plasma esterases.	By hydrolysis.
Stability	Hydrochloride salt is stable.	Forms stable salts with hydrochloric acid.	Stable.	Similar to procaine
Onset of action	5 minutes	Similar to tetracaine	Similar to procaine.	More rapid than with procaine.
Dose	As .25% solution topically	0.4% solution 1 or 2 drops in each eye.	Similar to procaine. Uses same as for procaine.	Similar to procaine.
Remarks	Produces spasmolytic action used I.M. Not used for injection. Used for topical anesthesia in lower urinary tract.	A para-amino benzoic acid ester Similar to procaine, except that a $C_4H_9O$ group is in position 3 of aromatic nucleus. Used for topical anesthesia of eye. Differs from symplocaine. (WIN 5706) which has butoxy in position 2.	No effect topically Systemic reactions less frequent than procaine. Structure same as procaine except a Cl appears in position 2 on aromatic nucleus.	Produces bacteriostatic properties. Same as procaine except a OH appears on position 2 of aromatic nucleus.

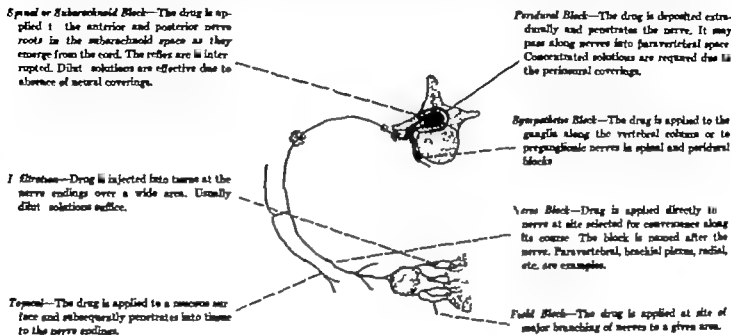
Name	Metahydroxy procaine	Carbocaine	Bupivacaine	Hydroxytetracaine
Synonym		WTN 9135	Propoxycaïne, Pruvacaine	Rbenocaine
Chemical structure	3, hydroxy procaine	di N-methyl-piperidine acid 2,6, dimethyl amide.	Same as procaine, except that a propoxy group is on position 2	OH in position 2 of tetracaine
Properties	Used as the sodium salt.	Similar to lidocaine. Forms a hydrochloride	Stable, white powder M.P. 184°C. Forms a 20% solution in water	Forms a hydrochloride
Potency	Slightly more than procaine	Take that of procaine, somewhat greater than lidocaine	Surface action twice as potent as cocaine. Similar to tetracaine for injection.	Less than tetracaine
Toxicity	Slightly less than procaine	Approximately twice that of procaine but less than lidocaine	Twice as toxic as tetracaine.	One-third as toxic as tetracaine.
Detoxification	Presumably similar to procaine	Slowly hydrolyzed.	By hydrolysis in liver and plasma.	Presumably by hydrolysis
Stability	Similar to procaine	Chemically allied to lidocaine. As amide and not as ester	Boilable, stable. Used as hydrochloride pH—4.5	Less stable than tetracaine
Onset of action	Similar to procaine	Similar to procaine. Duration similar to lidocaine.	Similar to procaine. Diffuses rapidly through tissues.	Used for topical anesthesia.
Dose	Similar to procaine.	1%, 1 and 2% solution.	0.1% infiltration.	
Remarks	Same as OH in position 3 on aromatic nucleus of procaine.	Used for infiltration and nerve block. Possesses some vasoconstrictor activity	Inactivated by glucose. Inositol used instead. Compatible with epinephrine.	

Name	Dyclonine	Prilocaine	Narcaine	Dicarbinoxide
Synonym	Dyclone, Falcaine	Tromethane	Amylase	Quetaine
Chemical structure	4, butoxy 3, piperidine propiophenone	4(3-p butoxy phenoxy propyl) morpholine hydrochloride	N amylamine ethyl para-amine benzoate hydrochloride	2, butyl 1, dimethyl amine ethoxy isopropylamine hydrochloride
Properties	White powder soluble in water. Forms hydrochloride.	White powder soluble in water.	White crystalline bitter powder. Soluble in water and alcohol.	White powder. Bitter warming taste and aromatic odor. Stable in alcohol and water.
Potency	Similar to cocaine topically	Low potency. Similar to benzocaine.	Similar to cocaine.	Less than dyclonine, greater than cocaine.
Toxicity	Low human toxicity. Oral or IV doses cause no circulatory respiratory effects. Not convulsant.	Low toxicity. Sensitizing potential low.	Convulsant, similar to cocaine.	Not established. Greater than cocaine. Not used except on skin.
Detoxification	Not altered in body	Not established.	Presumably by hydrolysis.	Presumably by hydrolysis.
Stability	Hydrochloride salt stabilizes with chlorbutanol. Heat labile. Not to be boiled.	Hydrochloride salt stable in air. pH of solution is acid.	Hydrochloride salt stable in air. pH—8.8-9.	Hydrochloride salt stable in air. pH 8.8-9.
Onset of action	Typically early. Long latent period, 5-10 minutes. Long duration once anesthesia established.	3-5 minutes	Within several minutes with smearing.	Few minutes, lasts 3-4 hours.
Dose	1% ointment or 1-2% solution topically	For anesthesia on skin or rectum (1% ointment)	0-4% solution 1-4 drops in eye.	0.5% lotion or ointment on skin.
Remarks	To be used topically only. Not for injection. Concentrations greater than 1% cause necrosis. Has been used I.V. 0.1% solution in amounts up to 5-10 cc. Bacteriostatic. Self-neutralizing. Does not have acidic or ester type. Included in N.N.R.	Not for ocular, nasal or oral use or for injection. Included in N.N.R. Not an ester or amide.	Does not cause nausea or increase intra-ocular tension. A derivative of para-amine benzoic acid. Included in N.N.R.	Used on skin. Not recommended for injection or on mucous membranes. Included in N.N.R.

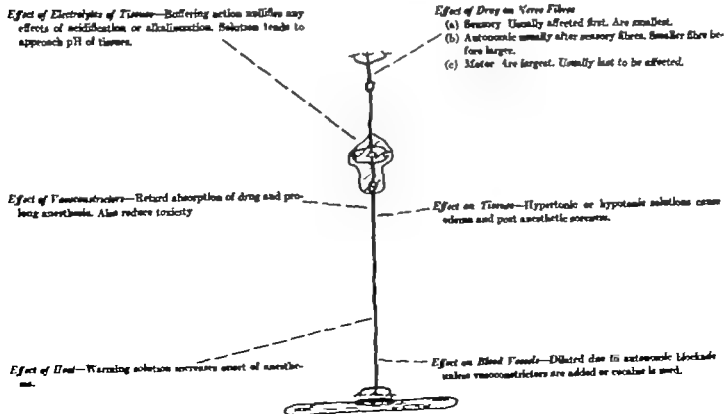
Name	Meprocaine	Clonidine	Metabuthetamine	Prilocaine
Synonyms	Orocaine			
Chemical structure	2, methyl 2, propargyl amino benzoate	2, isobutyl 2, methyl propargyl benzoate.	2, isobutyl amino ethyl meta amino benzoate.	diethyl amino 4, butoxy 2, amino benzoate.
Preparation	White powder M.P. 181°C. Hydrochloride salt.	White powder	White powder Melts at 184°C. Hydrochloride salt.	White powder Melts at 118°C. pH-4.5
Potency	Similar to procaine		Twice that of procaine.	Four times more potent than procaine.
Toxicity	Less than procaine.		2-3 times that of procaine.	About twice that of procaine.
Detoxification	Hydrolyzed rapidly in liver	Presumably by hydrolysis.	By hydrolysis in plasma and liver	By hydrolysis.
Stability	Hydrochloride is a white powder		Hydrochloride solutions not stable.	Very soluble. Forms a 7.5% solution.
Onset of action	More rapid than procaine. Duration similar to procaine.		Rapid like procaine.	Immediate. Lasts 1 1/2 hours.
Dose	2% solution for infiltration. Maximum 80 cc.		3.5% solution. Used in dentistry 80 cc. maximum.	1.5% solution 80 cc. maximum.
Remarks	Used largely in dentistry	Used in dentistry	More toxic than procaine. A meta amino benzoate.	A meta amino benzoate acid derivative.

## REGIONAL ANESTHESIA

Regional anesthesia, also known as conduction anesthesia, is accomplished by applying a local anesthetic drug to a nerve cell or fibre or ganglion and blocking efferent and afferent conduction from the site of application of the drug. Regional anesthesia is classified according to site of application of drug as follows:



## PHYSIOLOGY OF REGIONAL ANESTHESIA



## PHYSIOLOGY OF SPINAL ANESTHESIA

**Cortex**—Not affected. Depressed if blood pressure falls to shock levels. Consciousness may be lost.

**Respiratory Center**—Depressed during hypotension. Apnea results from ceasing cerebral activity.

**Vasomotor Center**—Active. Control of vessels in anesthetized area lost.

**Vagus Center**—Remains active. Vagal tone predominates in segments where sympathetic activity is abolished.

**Cough Center**—Remains active.

**Forming Center**—Ordinarily not affected. May be excited by:

- (1) Afferent impulses along vagi due to traction on abdominal viscera.
- (2) Cerebral activity secondary to hypotension.
- (3) Stimulation by drug which diffuses into cerebrospinal fluid.

**Cerebro-vascular System**—Not affected.

**Cerebral Blood Flow**—Depressed if level extends to D1.

**Lungs**—Slight increase in respiratory rate. Intercostal muscles paralyzed in "high spinal." Not affected in "low spinal." Paralysis at intermediate level. Minor volume exchange may decrease. Decreases in "high spinal." No effect on alveoli. Bronchi may constrict in "high spinal" due to predominance of vagal activity.

**Metabolism**—Decreased due to decreased muscle activity.

**Diaphragm**—Increased activity to compensate for intercostal paralysis in "high spinal." Diaphragmatic activity returns before intercostal activity in total spinal block.

**Adrenal**—Epinephrine content depleted. Not the cause of hypotension.

**Liver**—No significant change in function unless severe hypotension follows and remains untreated.

**Bile**—Unchanged.

**Kidney**—No change effect upon glomerular filtration, tubular reabsorption, or secretion. Urine continues to form during anesthesia. Overdistention of bladder may result during surgery.

**Bladder**—Atony during and loss of stimulus to void often leads to retention of urine in postoperative period. Cystometric studies reveal increase in bladder capacity.

**Sphincters**—Relaxed.

**Rectal Muscles**—Complete relaxation in anesthetized area. Log volume increased due to relaxation and pooling of blood in vessels.

**Body Temperature**—Decreased from loss of control of heat regulating center, decreased muscle activity and cutaneous vasodilatation.

**Intercostal Pressure**—Not affected. Increased during straining. Post lumbar puncture headache frequent. Cause not known.

**Eyes**—Not affected. Diplopia may result from paralysis of 4th or 6th nerve postoperatively.

**Cranial Nerves**—Not affected. Palsies may occur postoperatively. Cause not known.

**Face**—Pallor due to vasoconstriction. Sweating in unanesthetized area.

**Salivary Gland**—Not affected.

**Pharynx and Larynx**—Not affected.

**Heart**—Myocardium and conduction tissues not affected. Bradycardia prominent. Cardiac output decreased 10% or more. Stroke volume decreased. Circulation those prolonged 100%. Cardio-accelerator nerves depressed. Vagi remains active.

**Blood Pressure**—Systolic falls; diastolic falls slightly or is sustained. 1 or slightly below pre-anesthetic level. Decreased cardiac output and decreased stroke volume from failure of venous circulation. Renal and splanchnic arterioles under autonomic control do not dilate; peripheral arterioles under sympathetic control do dilate. More pronounced fall in high spinal anesthesia and hyper and hypotension. Pulse pressure markedly reduced.

**Venous Return**—Decreased due to relaxation of muscles in the extremities, reduced negative pressure from decreased thoracic movements and change in intra-abdominal pressure.

**Gastrointestinal System**—Bowel constricted. Increased tone and peristalsis due to parasympathetic predominance when sympathetic activity is abolished.

**Pancreas**—No effect on secretion or blood analysis or other pancreatic function.

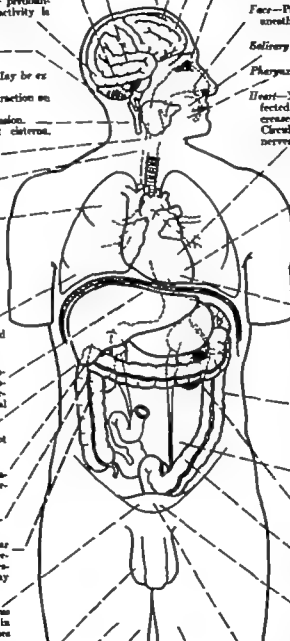
**Spleen**—Increased in size two or three times if of normal structure.

**Lymphatics**—No increase in absorption of "toxic" substances released by peritoneal cavity if peritonitis is present.

**Uterus**—No loss of uterine tone or motility. Pain of contractions relieved by blocking segments below D10. Contractions inhibited above D10.

**Fetus**—No effect on fetus. Breath spontaneously without resuscitation in uncomplicated obstetrics.

**Skin**—Vessels dilated from loss of sympathetic activity. Temperature rise as much as 10°F. Absence of sweating in anesthetized area. Marked pallor in unanesthetized portions.



**Blood Volume**—Not significantly altered. Disparity between blood volume and vascular space occurs from vasodilatation. Corrected by administration of vasoconstrictors rather than fluids.

**Non-protein Nitrogen**—Unchanged.

**Oxygen Capacity**—Unchanged if circulatory depression is overcome.

**Serum Protein**—Unchanged.

**Oxygen Content**—Slightly increased in arterial blood. Decreased in venous blood. Widened A-V difference may cause tissue anoxia.

**Urea**—Unchanged.

**Red Blood Cells**—No change or slight increase.

**Blood Glucose**—Not affected. May increase if hypotension remains uncorrected or vasoconstrictors are used.

**Leukocytes**—Polymorphonuclear cells increase during first twenty-four hours in post-anesthetic period.

**Carbon Dioxide Content**—Unchanged if respiration is not depressed.

**Bleeding Time**—Unchanged.

**Carbon Dioxide Combining Power**—Not affected.

**Clotting Time**—Unchanged.

## USES

1. For operations requiring extensive degrees of muscle relaxation.
2. For operations in which general anesthesia is contraindicated.

## CONTRAINDICATIONS

1. The presence of cardiac disease of all types, particularly coronary insufficiency or decompensation, or myocardial disease.
2. The presence of hypotension from any cause.
3. The presence of severe hypertension.
4. The presence of disease (infectious or otherwise) of the central nervous system.
5. The presence of anoxia from any cause.
6. The presence of states accompanied by decreased blood volume.
7. The presence of septicemia or infections about the vertebral column.
8. The presence of diseases characterized by marked increases in intra-abdominal pressure.
9. In psychically disturbed or apprehensive and uncooperative subjects.
10. The presence of diseases accompanied by reduction in pulmonary ventilation.

## ADVANTAGES

1. It provides excellent muscle relaxation.
2. It causes no significant blood chemical changes.
3. Soluble in a few basal anesthetic and inhalation anesthetics are contraindicated.
4. It allows use of cautery and electrical appliances during surgery.
5. It is inexpensive in comparison to other forms of anesthesia.

## DISADVANTAGES

1. It is non-controllable. Once it has been administered it cannot be withdrawn.
2. Possibility of failure cannot be fully excluded.
3. Not safe for surgery above the diaphragm.
4. Distressing circulatory disturbances are common.
5. Post-operative headache frequent.
6. Psychically unsuited for apprehensive patients.
7. Vagal pathways not blocked in abdominal surgery allowing undesirable reflex stimulation.
8. May be followed by various neurological complications, many of which are serious and permanent (myelitis, etc.).

## NEUROLOGICAL COMPLICATIONS OF SPINAL ANESTHESIA

**Headache**—Usually occurs after first day. Is usually intermittent, throbbing and aggravated by changes in posture. May last several days to months. Responds to analgesics, intrathecal injection of saline or peridural injection of saline. Believed to be due to leakage of cerebrospinal fluid from site of puncture.

**Meningitis**—Meningitis follows contamination from poor technique or inflammation due to chemical irritation.

**Myelomeningitis**—Usually occurs early. Believed to be due to chemical irritation. Difficult to differentiate from meningitis.

**Respiratory System**—Respiratory failure follows when drug ascends into thoracic and cervical segments, paralyzing intercostal muscles and diaphragm.

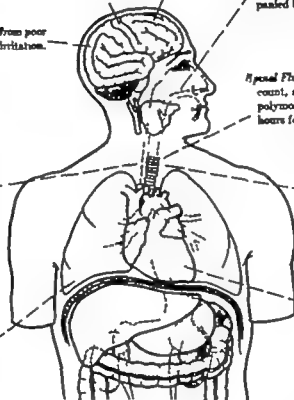
**Cranial Nerves**—Palsies transient in nature of IV, VI, VII and various components of spinal nerve. Occur after first 24 hours. May last up to 8 to 10 weeks. Not necessarily found in areas anesthetized by drug. Most often involves VI cranial.

**Cord**—Myelitis uncommon. Usually extends into cauda equina and causes permanent paralysis of the lower extremities. Is the most serious complication. Often associated with diseases of the spinal cord. Accompanied by fecal and urinary incontinence.

**Spinal Fluid**—Little or no significant change in cellular count, sugar or colloidal gold. Transient increase in polymorphonuclear cells and glucose during first 18 hours followed by a return to normal.

**Cells**—Toxic doses cause chromatolysis, dissolution of Nissl substance swelling of cell membrane with recovery after 80 days.

**Circulatory System**—Circulatory failure of neurogenic origin follows blockade. Severe hypotension not infrequent. Respiratory failure may follow due to cerebral anoxia.



## INTRINSIC FACTORS INFLUENCING LEVEL OF SPINAL ANESTHESIA

1. **Duration of Spinal Cord**—Fairly constant. Has little effect.
2. **Subarachnoid Volume**—Fairly constant. Has little effect.
3. **Length of Spinal Cord**—Varies. Dosage should be in proportion to number of segments to be anesthetized.

## FACTORS INFLUENCING DURATION OF SPINAL ANESTHESIA

1. **Chemical Nature of Drug**—Most important factor. Onset delayed with longer-lasting drugs.
2. **Dose of Drug**—Not important. Influences number of dermatomes involved. Duration increases up to a given point as dose increases beyond which increase in dose is ineffective.
3. **Response of Tissue to Drug**—Intensity and duration vary with individuals.
4. **Presence of Vasoconstrictors**—Epinephrine added to agent prolongs duration up to 60%. Pituitrin and nor epinephrine equally as effective. Ephedrine not effective.

## EXTRINSIC FACTORS INFLUENCING LEVEL OF SPINAL ANESTHESIA

1. **Rate of Injection**—The faster the rate the higher the ascent.
2. **Volume of Solution**—The greater the volume the greater the spread of solution in spinal segments.
3. **Concentration**—The greater the total dose the greater the number of segments involved and the greater the intensity of anesthesia.
4. **Site of Injection**—Must be low for distribution involving only lumbar or sacral segments.
5. **Specific Gravity of Solution**—Hyperbaric solutions gravitate downward, hypobaric upward, isobaric variable.
6. **Position of Patient**—Hyperbaric solutions migrate cephalad. Hypobaric solution caudad in head-down position.

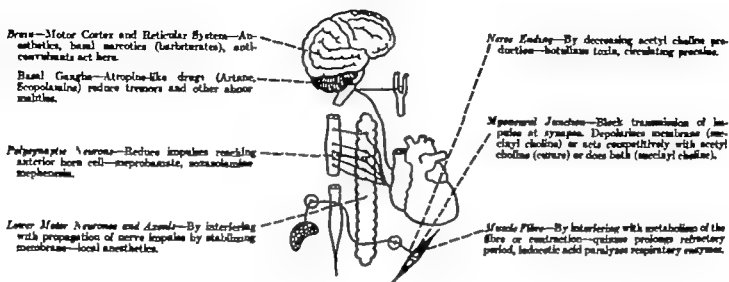


## SECTION XII NON ANESTHETIC DRUGS USED IN CONJUNCTION WITH ANESTHESIA

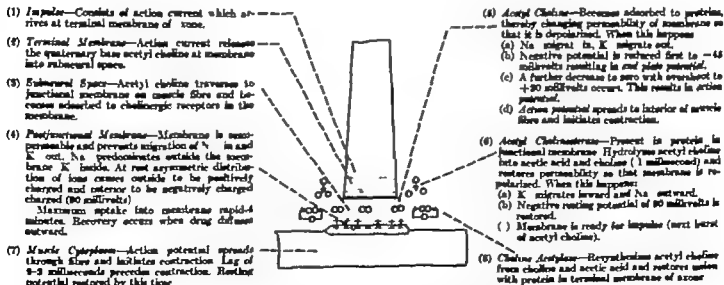
### SKELETAL MUSCLE RELAXANTS

#### POSSIBLE SITES OF ACTION ON MOTOR SYSTEM

Muscle tone may be decreased by drugs acting at the following sites



#### MECHANISM OF NEUROMUSCULAR TRANSMISSION

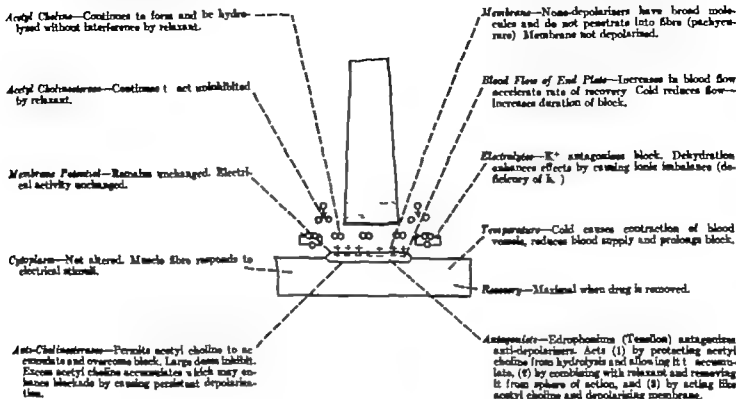


#### MECHANISM OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS

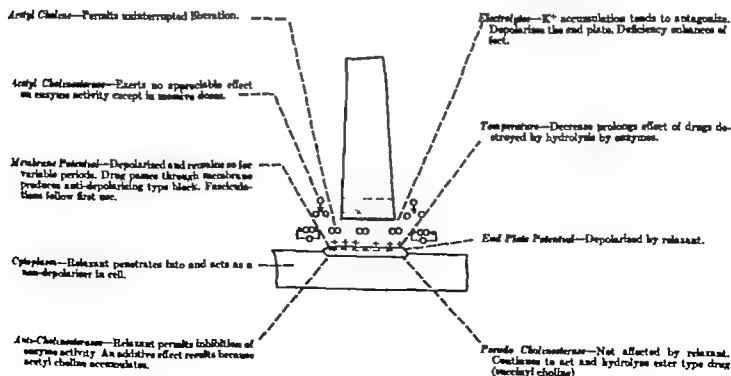
**Mechanism of Neuromuscular Block**—Neuromuscular transmission is inhibited by: (1) anti-depolarizing drugs. These are preferentially bound to cholinergic receptors. They do not possess the action of acetyl choline but prevent acetyl choline from depolarizing. They act by competitive inhibition. (2) Depolarizing drugs. These are quaternary bases which act similarly to acetyl choline but for a longer time thereby

causing permanent depolarization which prevents contraction followed by the fasciculation. (3) Drugs causing dual block. Membrane first becomes depolarized but the drug penetrates into fiber and acts as non-depolarizer even though the membrane potential is restored. Also known as biphasic block.

PHYSIOLOGICAL ALTERATIONS AT END PLATE CAUSED BY ANTI-DEPOLARIZERS (NON DEPOLARIZERS)



PHYSIOLOGICAL ALTERATIONS AT END PLATE CAUSED BY DEPOLARIZING BLOCKING AGENTS



## CHEMISTRY OF NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents are quaternary bases (R<sub>4</sub>NOH) derived from nitrogen. Few are tertiary amines (erythroidine alkaloids). Other polyvalent elements (arsenic, phosphorus, bismuth) may form bases which act qualitatively similarly. Group is called "onium" group. Blockade probably due to the positively charged ion. Mono and tri-quaternary bases (Gallamine) may have curarimimetic activity but they are in the minority. The majority are di or bis-quaternary bases. They have two nitrogen atoms with valence of 8 and the following characteristics:

- (1) Nitrogen atoms are approximately 14 Å (10 carbon atoms) apart.
- (2) They form salts with acids (hydrochloric, hydroiodic and hydrobromic).
- (3) Straight chain compounds are usually referred to as "methonium" derivatives.
- (4) They are allied to ammonium hydroxide. The hydrogen atoms are replaced by methyl groups.
- (5) Cyclic structures whose combined length when placed in succession maintains the nitrogen atoms the conventional distance of 14 Å.
- (6) Two types of molecules—slender and broad. Slender molecules (tubocurarine) penetrate the synovial junction while broad (pachycurarene) do not.
- (7) They ionize and yield a positively charged cation and anion. The cation causes the relaxation and forms an ionic bond with the cholinergic receptor.
- (8) Methyl substitution of the nitrogen atom confers greater neuromuscular blocking action than ethyl. Ethyl substituted compounds show greater ganglionic blocking effect.
- (9) Quaternary bases penetrate blood brain and epithelial barriers poorly. Absorption is poor. They pass through the placental membrane.
- (10) They are eliminated unchanged or detoxified slowly by the liver.

### DISTRIBUTION IN TISSUES

Rate of curarization and recovery are dependent upon the ability of the drug to diffuse in and out of the receptor substance. After an intravenous administration:

- (1) The highest plasma concentration is attained shortly after termination of the injection.
- (2) Paralysis develops when the concentration necessary to produce block penetrates the end plate membrane.
- (3) Uptake at end plate is preferential to other tissues and occurs quickly.
- (4) The peak concentration at the end plate is attained in a relatively brief time interval compared to peak in other tissues (3 or 4 minutes versus 1 hour) for tubocurarine.
- (5) Little of the relaxant is decomposed or excreted while block is in progress.
- (6) The neuromuscular block is terminated after re-entry of drug from end plate to plasma.

Degree of blockade varies with:

- (1) Mode of administration. I.V. yields response more rapid and more intense than I.M.
- (2) Distribution, excretion and metabolism of the drug.
- (3) Body temperature (cold reduces blood supply or enzyme activity)
- (4) Electrolyte imbalance and state of hydration (K deficiency enhances effect)

### Uses of Muscle Relaxants

1. As an adjunct to anesthesia to obtain muscle relaxation.
2. To "soften" convulsions during electroshock therapy.
3. To deliberately produce apnea when indicated in resuscitation (Iron Lung, chest surgery, etc.)
4. To relieve laryngeal spasm.
5. To relieve spasm in disease states (tetanus, rabies)

### Advantages of Relaxants

1. Allows use of lighter planes of anesthesia or use of hypnotic agents (N<sub>2</sub>O).
2. Have no central depressant effect.
3. No after-effects (resonance)

### Disadvantages

1. Causes hyperventilation along with surgical relaxation.
2. Repeated doses required, cumulative effects result.
3. Influenced by disturbances in electrolyte balance.
4. Produces apnea of obscure etiology uncorrected.
5. Muscles relax postoperatively (depolarizing type)
6. Complete muscle activity not fully recovered for many hours after apparent return of tone.
7. Antagonists either not available or not fully reliable.

## COMPLICATIONS USING MUSCLE RELAXANTS

### A. VASCULAR

#### 1. Hypotension

- (a) From ganglionic blockade using excessive doses of relaxant itself.
  - (b) From histamine release.
  - (c) From decreased venous return from (1) pooling of blood in the relaxed muscle, (2) decreased thoracic and abdominal compliance or (3) positive pressure on airway (contracted respiration)
  - (d) From vagolytic action—tachycardia with decreased cardiac output (Gallamine)
  - (e) Overdose of antagonists causing parasympathetic blockade.
- #### 2. Bradycardia and Cardiac Arrest
- (a) Use of parasympathetic antagonists (atropine) without preliminary use of atropine.
  - (b) Use of benzocyclonium (bradycardia from vagal action)
- #### 3. Tachycardia
- (a) Vagolytic action (Gallamine)
  - (b) Anti-cholinergic drug mixed with antagonist or its parasympathetic effect.
- #### 4. Hypertension
- (a) Relative inhibition of cardiac vagus giving tachycardia and elevation in blood pressure.
  - (b) Inadequate ventilation causing hypercarbia.
  - (c) Ganglionic stimulation of weak agents.

### B. RESPIRATORY

#### 1. Hyperventilation, Apnea

- (a) Overdose of drug causing sustained peripheral effect.
- (b) Delayed excretion (renal and liver disease).
- (c) Electrolyte imbalance (acidosis) causing hypotension.
- (d) Potentiation by anesthetic (ether) antibiotics (neomycin).
- (e) Muscular disease (myasthenia gravis).
- (f) Decreased somewhat cholinesterase (using eserilyl choline)
  - (i) in liver disease.
  - (ii) after multiple transfusions.
- (g) Cumulative effects (diatropine, mivacurium, succinyl choline).
- (h) Overdose of antagonists (atropine).
- (i) Central depressant action (tubocurarine).
- (j) Combination of respiratory depressant plus non-depressant.
- (k) Over-ventilation giving rise to hypoxemia and stimulation of Hering-Breuer reflex.
- (l) Re-distribution of cumulated drug causing re-curarization.

#### 2. Incidental to But Not as Result of Neuromuscular Agent

- (a) Hypocarbica from over-ventilation.
- (b) Anemia—cerebral.
- (c) Hypovolemia with inadequate perfusion of tissues (shock).
- (d) Hypothermia resulting in decreased metabolism or excretion of drug.
- (e) Depression due to succinyl and other C.N.S. depressants.
- (f) Reflex apnea—endotracheal tube, manipulation of view, etc.

#### 3. Bronchospasm

- (a) Histamine release—use antihistamine prior to and epinephrine during.
- (b) Parasympathetic stimulation from antagonists—combine with atropine.
- (c) Instrumentation without obtaining bronchial reflex with topical anesthetic.

### C. EXCESSIVE SALIVATION

- (a) Parasympathetic drugs (atropine)
- (b) Benzocyclonium.
- (c) Inability to swallow due to paralytic muscles (succinylcholine patients—without atropine).

### D. SKIN RASHES

- (a) Use of salts formed from hydroiodic acid and hydrobromic acid.

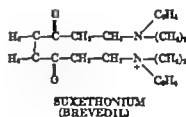
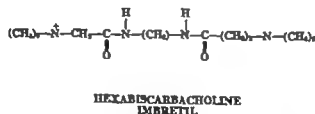
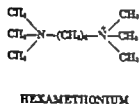
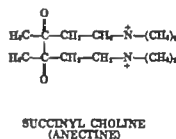
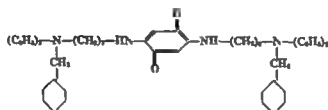
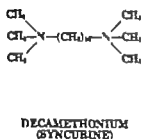
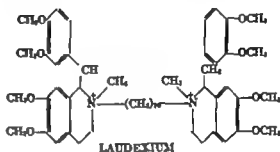
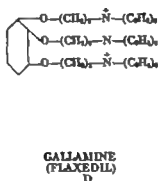
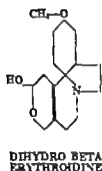
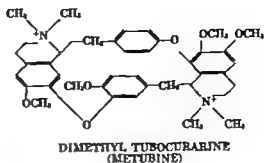
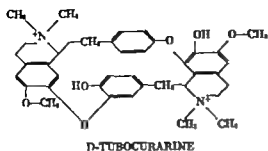
### E. INCREASED MUSCLE ACTIVITY

- (a) Facilitation following use of depolarizing drug.
- (b) Increased intra-ocular tension with use of succinyl choline causes tetany of eye muscles.
- (c) Muscle pains and cramps following depolarizing drugs which cause fasciculations.

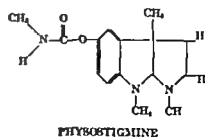
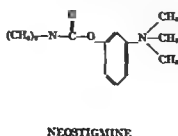
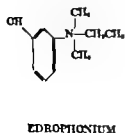
### F. VISCERAL EFFECTS

- (a) Dilated bowel due to ganglionic blockade (diatropine).

## CHEMICAL STRUCTURE OF SKELETAL MUSCLE RELAXANTS



## CHEMICAL STRUCTURE OF ANTAGONISTS TO MUSCLE RELAXANTS



# THE PHARMACOLOGY OF ANESTHETIC DRUGS

## CURARE AND TUBOCURARINE

**HISTORY**—First report of its use as an arrow poison brought to Europe by Sir Walter Raleigh in 1595. Various preparations derived from miscellaneous plants principally of strychnos family constituted older preparations. Lack of a dependable and identifiable source of drug and absence of standardized specimens interfered with satisfactory clinical use.

**SOURCE**—Northwest basin of Orinoco Valley. Natives mixed many plants, at least 5 species of strychnos, which were source of earlier specimens. Gill's specimen obtained exclusively from chondrodendron tomentosum a species of menispermaceae plants known to Chazotte Indians as "ampi huasa."

**APPLICATION OF DRUG**—Richard Gill, naturalist and explorer in 1838 brought to United States from South America a curare specimen of identifiable plant origin (chondrodendron tomentosum). In 1848 Wintersteiner and Dutcher (Squibb Institute) isolated the active principle, an alkaloid known as d-tubocurarine from the preparation. Antivenereal curare was first studied by A. E. Bennett and A. R. McIntyre who introduced its use for shock treatment. Antivenereal introduced into anesthesiology by H. R. Griffith and G. E. Johnson, Montreal in 1942 subsequently by S. C. Cullen, Iowa, in 1944 at suggestion of Lewis H. Wright, New York. Classical curare effect was first described by Claude Bernard in 1840.

**Mode**—Acts by competitive inhibition with acetyl choline. Prevents acetyl choline from acting but has no action of its own. Elevates threshold to acetyl choline at synapse. Inhibits acetyl choline formation at any synapse. Inhibits activity of cholinesterase. Muscle responds to direct electrical stimulation but no depression occurs at end plate. Activity of neuromuscular junction is not depressed. Does not act on smooth muscle.

**Sensory Error**—Conduction not abolished. Acetyl choline liberation not inhibited. Not antagonized by atropine.

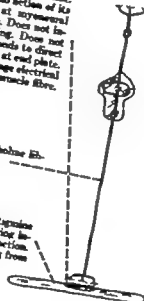
**Cholinesterase**—No effect on ester or enzyme. Physostigmine and neostigmine inhibit cholinesterase, thereby favoring increase of acetyl choline and antagonism of paralytic action. Edrophonium antagonism blockade by displacing drug from receptor.

### USES

1. As an adjuvant to general anesthesia to secure relaxation without causing deep anesthesia.
2. To alterate muscle spasm in convulsive shock therapy and relief of convulsive convulsions by excitation of nervous system.
3. As a diagnostic test for strabismus.
4. To overcome spasm of strabismus.
5. To produce respiratory paralysis in disease of nervous and various types and pelvic examinations.
6. To secure relaxation for manipulative procedures, endoscopy of various types and pelvic examinations.
7. To supplement spinal anesthesia when motor effects are passing off.

### CONTRAINDICATIONS

1. Myasthenia gravis.
2. Shock from trauma or hemorrhage.
3. Respiratory obstruction, depression or failure.
4. Renal disease.
5. Dehydration accompanied by electrolyte imbalance & deficiency potassium action.



**Preparation**—Bark and stems of plant chondrodendron tomentosum extracted with water, then alcohol, evaporated to dryness and made into a sterile solution, having a pH of 4.6. Manufactured in rabbits using the "Hend Drop" method. D-tubocurarine chloride pentahydrate is now an accepted standard. One milliliter of curare 0.15 mgm. of alkaloid.

**Chemistry**—Active principle is the alkaloid d-tubocurarine, quaternary ammonium base which forms hydrochloride salt. Molecule is broad (pachycurare). Does not enter muscle fibre.

**Pharmacology**—Acts on receptor substance of striated (voluntary) muscle.

**Onset of Action**—Intravenously within 3 minutes, intramuscularly 15 minutes, orally no effect unless renal excretion is impaired.

**Duration**—Varies. 1 non-neurotic subject a curarizing dose produces an effect lasting 90 to 120 minutes. With anesthesia action may last 40 to 60 minutes.

**Spinal Anesthesia**—Response varies considerably with species. In man produces non-depolarizing block.

### DISADVANTAGES

1. Paralytic dose causes death by asphyxia.
2. Antidote not always effective when subject is completely curarized.
3. Action transient.
4. Convulsive effects follow repeated doses.
5. Prolonged use may result in haemorrhage.
6. Not effective when orally administered.

### ADVANTAGES

1. Relaxation obtained & still without deepening anesthesia.
2. Allows higher plane of anesthesia to be maintained with all agents.
3. Allows mild anesthesia such as N<sub>2</sub>O and G<sub>2</sub> to be used for surgery.
4. Allows muscular relaxation.
5. Avoids arrhythmias.
6. Relaxation may be obtained rapidly—within several minutes after administration.
7. No intolerance to repeated use.

### PREPARATION AND DOSES

Chondrodendron extract (tubocurarine, curare)—60-80 units intravenously in 10 milliliter fractions of 5 minutes or d-tubocurarine chloride in aqueous solution. Units 90-100 0.1 mgm. = 1 cc.

**Cerebrum**—Subparalytic doses cause no depression. Some depression with paralytic doses. Pain perception, memory and other cerebral reactions remain active. Reaction to pain inhibited due to paralytic action. No change in electro-encephalogram.

**Temperature Regulating Center**—Not affected.

**Vasomotor Center**—No significant effect with therapeutic doses.

**Facial Center**—Not depressed. Involuntary muscles involving eyelids remain active in unanesthetized subjects.

**Respiratory Center**—No significant effect with therapeutic doses.

**Vagus Nerve**—Greater than paralytic doses depress and delay transmission to effector cell.

**Cough Center**—Not affected. Coughing inhibited due to paralysis of thoracic muscles.

**Lungs**—No effect. No contact of drug with alveoli. Death may result from asphyxia due to paralysis of respiratory muscles without artificial respiration in complete curarization.

**Bronchi**—No action on bronchi. Bronchoconstrictor action may follow exceptional cases due to histamine-like action of drug.

**Myotonia**—Reduced due to decreased muscular activity.

**Intercostal Muscles**—Paralyzed before diaphragm.

**Diaphragm**—Last voluntary muscle to be paralyzed, first to recover.

**Liver**—Drug partly detoxified here. Benzaldehyde eliminated unchanged by kidney into urine. Effects on hepatic function negligible.

**Kidney**—Unchanged portion eliminated in the urine. Urinary fraction possesses curare-like action. Cumulative action follows use in renal damage. Basic is true of tubocurarine. Second dose more effective than first dose even when effects of first dose are gone.

**Body Temperature**—Reduced due to decreased muscular activity.

**Blood**—No significant effects. After prolonged administration hemocoagulation followed by circulatory collapse occurs.

**Skin**—Perception of pain and other sensation not abolished. No sweating. May produce typical histamine wheals.

**Tissues**—No tissue changes attributable to drug.

**Eyes**—No effect on pupils. Muscles of lids and eyeballs first to be involved. Heaviness of lids, ptosis, diplopia, nystagmus follow in order in conscious subjects. Relaxation and cessation of eyeball movements in anesthetized subjects.

**Facial Nerve**—Next to the eye in involvement. Causes mask-like expression on face.

**Trigeminal Nerve**—Not affected—partly sensory.

**Salivary Glands**—Secretions continue to form in unanesthetized patient.

**Neck Muscles**—Depressed after cranial nerves.

**Pharynx**—"Gas" reflex abolished due to loss of motor control of pharyngeal muscles.

**Muscles of Swallowing**—Affected early. Saliva and other secretions accumulate in pharynx due to absence of power of deglutition.

**Larynx**—Coughing abolished due to loss of expiratory power from paralysis of thoracic muscles. Vocal cords relaxed. Sensory effects of larynx not affected.

**Heart**—No significant effects. No effects on electrocardiogram. Does not prevent arrhythmias.

**Blood Pressure**—Therapeutic doses cause no significant effects.

**Stomach**—Decreased tone. Decrease in peristalsis. Drug probably destroyed in gastrointestinal tract. Ineffective orally.

**Intestines**—Paralytic doses decrease muscle tone and peristalsis.

**Uterus**—Not relaxed by therapeutic doses. Believed to pass into placental circulation.

**Muscles of Extremities**—Affected after the abdominal and thoracic muscles.

**Muscle Fibers**—React to electrical stimulation. No direct effect on muscle.

**Nerve Endings**—No effect. No inhibition of acetylcholine production.

**Autonomic Nervous System**—Causes a depression of (from pre- to post-ganglionic fibers) conduction through autonomic ganglia both sympathetic and parasympathetic. Does not prevent liberation of acetylcholine when preganglionic fiber is stimulated. Large dose may also prevent transmission from postganglionic fibers to effector cell.

THE ACTIONS OF CURARE ARE ESSENTIALLY THOSE OF TUBOCURARINE

## SUCCINYL CHOLINE

**SYNONYMS**—Anectine (Wellcome), succinethonium, Quelicin, Succostrin (Squibb)

**HISTORY**—First studied in curarized animals by Hunt and Taveau in 1911 and thereby muscle relaxant effects were overlooked. Relaxant effects discovered by Bovet and co-workers in 1931. Numerous investigators have studied action since then. (Folkes et al.)

**CHEMISTRY**—A di-quaternary base consisting of two acetyl choline molecules fused together. Addition of carboxyl groups to a quaternary base shortens duration of action. Nitrogen atoms 14Å apart.

**PROPERTIES**—White odorless, slightly bitter powder. Forms a hydrate which melts at 155°-160°. Very soluble in water, slightly soluble in benzene and chloroform, insoluble in ether. Prepared as the di-hydrochloride and di-iodide. pH of 2% solution varies between 2-3. Incompatible with alkalis, thiopental and other sodium barbiturate solutions. Chloride preferred—does not cause sodium. Iodide  $\frac{1}{2}$  as potent (1 mg. = 1 mg.) as hydrochloride. Stable. Sterilized by autoclaving. Solutions lose potency unless refrigerated.

**Cerebrum**—Not depressed. Electroencephalogram remains unchanged. Anesthetic remains clear in unanesthetized patients. No effect on motor neurons.

**Forming Center**—Not affected. No postoperative nausea and vomiting.

**Thermoregulatory Center**—Not affected. Body temperature may fall due to decreased heat output from decreased muscle activity.

**Vasomotor Center**—Not affected. Effects on vascular system are peripheral.

**Respiratory Center**—Ordinarily not affected. Apnea may develop. Apnea due to peripheral blockade of respiratory muscles, adrenergic drugs (morphine) or hyperventilation, or low anesthetic level.

**Vagus Center**—Not affected. Any effects on parasympathetic system.

**Cough Center**—Not affected. Coughing inhibited due to paralysis of thoracic muscles.

**Lungs**—No direct effect. Hering-Breuer reflex intact. Easier to inflate due to loss of resistance of thoracic muscles. Hyperventilation or apnea results necessitating controlled or assisted respiration.

**Branches**—No direct effect. No histamine release of clinical significance. Bronchi reflex remains active. Sputum possible from local stimulation or irritation.

**Eyes**—No effect on pupils. Lids relaxed. Extra-ocular muscles develop tetanic state constricting eyeballs causing increased intra-ocular tension. This muscle group responds like sympathetic muscles due to drug.

**Facial Nerve**—Not affected. Erection remains active.

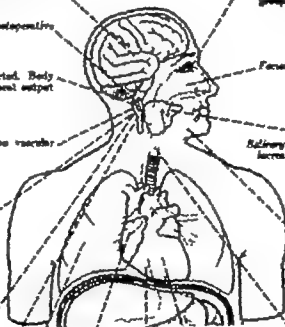
**Salivary Glands**—Continue to secrete but amount not increased. Atropine inhibits.

**Pharynx**—Gag reflex abolished due to loss of motor control of pharyngeal muscles. Breathing abolished. Secretions continue to form and accumulate in pharynx.

**Larynx**—Vocal cords relaxed. Secondary effects of larynx not affected.

**Heart**—No significant effects. No effect on myocardium. Does not cause or prevent arrhythmias. Does not increase systemic tension.

**Blood Pressure**—Large drops occur transient elevation possibly due to sympathetic stimulation. Also may arise from CO<sub>2</sub> retention. Hypotension uncommon.



**Myelinium**—Decreased due to decreased muscle activity

**Diaphragm**—More resistant than other muscles. First to resume activity

**Liver**—No effect on function. Drug rapidly destroyed in plasma by enzymes (pseudo cholinesterases) elaborated here. Liver diseases cause decrease of enzymes, may be responsible for prolonged apnea.

**Fat**—Hydrolyzed to succinyl monocholine and succinic acid in plasma. Monocholine hydrolyzed 8-10 times more slowly. May accumulate in tissues and cause blockade. Alkalosis favors hydrolysis of both esters.

**Adrenal**—N. known effect.

**Kidney**—N. effect on renal function. 8-16% excreted into urine by glomerular filtration. Renaloid hydrolyzed. N. histologic changes.

**Bladder**—No known effect

**Card**—Does not affect synapses or motor centers.

**Body Temperature**—Reduced due to decreased muscular activity. Destruction retarded by decrease in temperature due to decreased enzymatic activity.

**Blood**—No significant changes in composition, volume or cell morphology. Destroyed in plasma.

**Nerve**—No resending. N. histamine released in a break. Perception of pain, temperature and other sensations mediated by cutaneous end organs remains active.

**Antagonists**—No suitable antagonists. Antagonizes tubocurarine and myasthenia gravis. Potentiated by neostigmine, physostigmine, acetylcholine and related drugs and decamethonium. After prolonged use may act like non-depolarizing drug and be enhanced by non-depolarizers and antagonized by edrophonium. Potassium ion enhances the effect.

**Gastro-intestinal**—N. effect on tone and activity of stomach, intestines or upon secretions. Not absorbed or effective orally or rectally.

**Spleen**—No known effect.

**Uterus**—No effect on uterus. Believed to pass placenta but hydrolyzed before it reaches fetus.

**Muscle**—Acts by persistent depolarization (Phase I). Arms beyond membrane also becomes inactivated. Causes fasciculations initially. Penetrates into the myoneural membrane. Membrane potential restored to normal. Not enhanced by ether cyclopropane or other anesthetics. Painful and acting muscles in post-operative period follow rapid, initial administration.

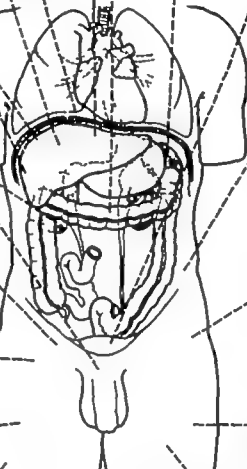
Succinyl monocholine also depolarizes. Accumulation may cause prolonged apnea. Repeated doses do not cause repetition of fasciculations. After prolonged use Phase II appears. Drug in fibers then acts like a non-depolarizer. Non-depolarizers re-enforce effect anti-cholinesterases antagonize phase II.

**Nerve**—Large doses inhibit true cholinesterase. Do not retard propagation of action currents. Acts on myoneural junctions. Does not inhibit release of humoral substances (acetylcholine).

**Autonomic Nervous System**—No significant effect on ganglia. Large doses block 400-700 times paralyzing dose necessary for ganglionic blockade. Ganglionic effect not overcome by atropine.

**Route of Administration**—Most effective and rapid acting by intravenous route. Absorbed by intramuscular and subcutaneous route but action comes on more slowly. Not effective orally. Ten times I.V. dose required intraperitoneally.

**Mode of Administration**—Rapid acting. Most effective and acts most rapidly intravenously. Administered by intravenous drip, continuously or in fractions in a solution containing 1 mgm. per cc. Single intravenous doses 20-40 mgm. in adults give duration of 8-8 minutes. Usually combined with thiopental (or like drug) and nitrous oxide. Lethal dose 1000 or more times depolarizing dose.





# THE PHARMACOLOGY OF ANESTHETIC DRUGS

## SUCCINYL CHOLINE

**SYNONYMS**—Anectine (Wellcome) succinethionium, Quelcin, Succotrion (Squibb)

**HISTORY**—First studied in curarized animals by Hunt and Taveau in 1911 and thereby muscle relaxant effects were overlooked. Relaxant effects discovered by Bovey and co-workers in 1951. Numerous investigators have studied action since then. (Foldes et al.)

**CHEMISTRY**—A di-quaternary base consisting of two acetyl choline molecules fused together. Addition of carboxyl groups to a quaternary base shortens duration of action. Nitrogen atoms 14Å apart.

**PROPERTIES**—White, odorless, slightly bitter powder. Forms a hydrate which melts at 158°-160°. Very soluble in water, slightly soluble in benzene, and chloroform, insoluble in ether. Prepared as the di-hydrochloride and di-sulfide. pH of 2% solution varies between 2-3. Incompatible with alkalis, thiopental and other sodium barbiturate solutions. Chloride preferred—does not cause sodium iodide f as potent (1 mg. = 1 mg.) as hydrochloride. Stable, sterilized by autoclaving. Solutions lose potency unless refrigerated.

**Cardium**—Not depressed. Electrocardiogram remains unchanged. Succinyl remains clear in use. Anesthetized patients. No effect on motor neurons.

**Respiratory Center**—Not affected. No postoperative depression and vomiting.

**Temperature Regulating Center**—Not affected. Body temperature may fall due to decreased heat output from decreased muscle activity.

**Vascular Center**—Not affected. Effects on vascular system are peripheral.

**Respiratory Center**—Ordinarily not affected. Massive doses may depress. Apnea due to peripheral blockage of respiratory muscles, sedative drugs (morphine) or hyperventilation, or low arterial level.

**Parasympathetic Center**—Not affected. Any effects on parasympathetic system.

**Cough Center**—Not affected. Coughing inhibited due to paralysis of thoracic muscles.

**Lungs**—No direct effect. Hering-Breuer reflex intact. Easier to inflate due to loss of resistance of thoracic muscles. Hyperventilation or press results necessitating controlled or assisted respiration.

**Branches**—No direct effect. No histamine release of clinical significance. Branchial reflexes remain active. Apnea possible from local stimulation or irritants.

**Eyes**—No effect on pupils. Lids relaxed. Extra-ocular muscles develop isometric static contracting spasm causing increased intra-ocular tension. This spasmic group responds like anesthetic muscle due to drug.

**Facial Nerve**—Not affected. Sensation remains active.

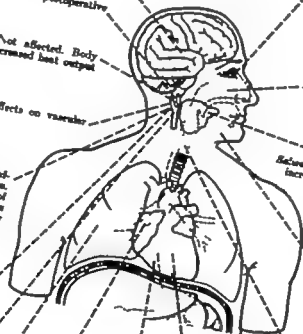
**Salivary Glands**—Continue to secrete but amount not increased. Atropine inhibits.

**Pharynx**—"Gag" reflex abolished due to loss of motor control of pharyngeal muscles. Swallowing abolished. Secretion continues to form and accumulate in pharynx.

**Larynx**—Vocal cords relaxed. Swallow of larynx not affected.

**Heart**—No significant effects. No effect on myocardium. Does not prevent arrhythmias. Does not stimulate uterine tissues.

**Blood Pressure**—Large doses cause transient elevation possibly due to sympathetic stimulation. Also may arise from CO<sub>2</sub> retention. Hypertension uncommon.



**Musculum**—Decreased due to decreased muscle activity

**Diaphragm**—More resistant than other muscles. First to resume activity

**Liver**—No effect on function. Drug rapidly destroyed in plasma by esterase (pseudo cholinesterases) elaborated here. Liver diseases cause decrease of enzymes, may be responsible for prolonged apnea.

**Fate**—Hydrolyzed to succinyl monocholine and succinic acid in plasma. Monocholine hydrolyzed 8-10 times more slowly. May accumulate in tissues and cause blockade. Alkalosis favors hydrolysis of both esters.

**Adrenal**—N. known effect.

**Kidney**—N. effect on renal function. 8-15% excreted into urine by glomerular filtration. Remainder hydrolyzed. No histologic changes.

**Bladder**—No known effect.

**Card**—Does not affect synapses or motor centers.

**Body Temperature**—Reduced due to decreased muscular activity. Destruction retarded by decrease in temperature due to decreased enzymatic activity.

**Blood**—N. significant change in composition, volume or cell morphology. Destroyed in plasma.

**Skin**—No sweating. No histamine released in wheals. Perception of pain, temperature and other sensations mediated by cutaneous and organ systems active.

**Antagonists**—N. suitable antagonists. Antagonizes tubocurarine and myasthenia gravis. Potentiated by neostigmine, physostigmine, acetylcholine and related drugs and decarboximines. After prolonged use may act like non-depolarizing drug and be enhanced by non-depolarizers and antagonized by edrophonium. Pilocarpine ion enhances the effect.

**Gastro-intestinal**—N. effect on tone and activity of stomach, intestines or upon secretions. Not absorbed or effective orally or rectally.

**Spleen**—No known effect.

**Uterus**—N. effect on uterus. Believed to pass placenta but hydrolyzed before it reaches fetus.

**Muscles**—Acts by persistent depolarization (Phase I). Arise beyond membrane also becomes inactivated. Causes fasciculations initially. Penetrates into the myoeccular membrane. Membrane potential restored to normal. Not enhanced by ether cyclopropyl or other anesthetics.

Initial and acting muscles in post operative period follow rapid, initial administration.

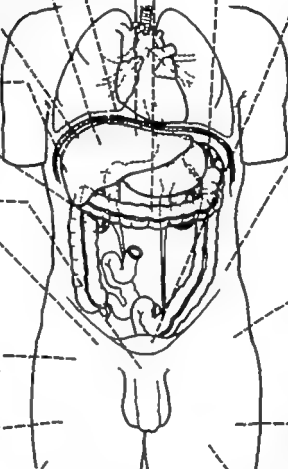
Succinyl monocholine also depolarizes. Accumulation may cause prolonged apnea. Repeated doses do not cause repetition of fasciculations. After prolonged use Phase II appears. Drug in fibers then acts like a non-depolarizer. Non-depolarizers reverse effect; anti-cholinesterases antagonize phase II.

**Nerves**—Large doses inhibit true cholinesterase. Do not retard propagation of action currents. Acts on pyrenousal function. Does not inhibit release of hormonal substances (acetylcholine).

**Autonomic Nervous System**—No significant effect on ganglia. Large doses block. 500-700 times paralyzing dose necessary for ganglionic blockade. Ganglionic effect not overcome by atropine.

**Routes of Administration**—Most effective and rapid acting by intravenous route. Absorbed by intramuscular and subcutaneous routes but action comes on more slowly. Not effective orally. Ten times I.V. dose required intraperitoneally.

**Modes of Administration**—Rapid acting. Most effective and acts most rapidly intravenously. Administered by intravenous drip, continuously or in fractions in solution containing 1 mgm. per cc. Single intravenous doses 50-80 mgm. in adults give duration of 15-30 minutes. Usually combined with thiopental (or like drug) and nitrous oxide. Lethal dose 1000 or more times depolarizing dose.



## DECAMETHONIUM (SYNCURINE)

SYNONYMS—Syncurine  $C_{10}$ 

**CHEMISTRY AND PROPERTIES**—A bi-quaternary base composed of 10 carbon atoms in a straight chain with a quaternary nitrogen atom on each terminal carbon. Three methyl groups on nitrogen atom. Forms halides with hydrobromic, hydrochloric and hydroiodic acid. Water soluble. Preparation contains 1 mgm. per cc. Solution is stable. Non-irritating to the tissues. Compatible with barbiturates (thiopental) in the same solution.

**Cerebrum**—Ordinarily not depressed. Electroencephalogram not altered. Awareness remains clear in non-anesthetized patients. Some central depression with massive doses.

**Eyes**—No effect on pupils. Lids relaxed. Extra-ocular muscles become irritable.

**Temperature Regulating Center**—Not affected. Body temperature may fall due to decreased heat output and decreased muscle activity.

**Trigeminal Nerve**—Not affected. Breathing remains.

**Vasomotor Center**—Not directly affected.

**Salivary Glands**—Continue to secrete. Secretions not increased.

**Vagus Center**—Not directly affected. No vagolytic effects.

**Pharynx**—"Gag" reflex abolished due to loss of motor control of pharyngeal muscles. Swallowing abolished. Secretions continue to form and accumulate in pharynx.

**Cough Center**—Not directly affected. Coughing inhibited due to paralysis of thoracic muscles.

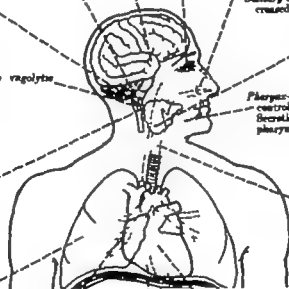
**Larynx**—Vocal cords relaxed. Sensory effects of larynx not affected.

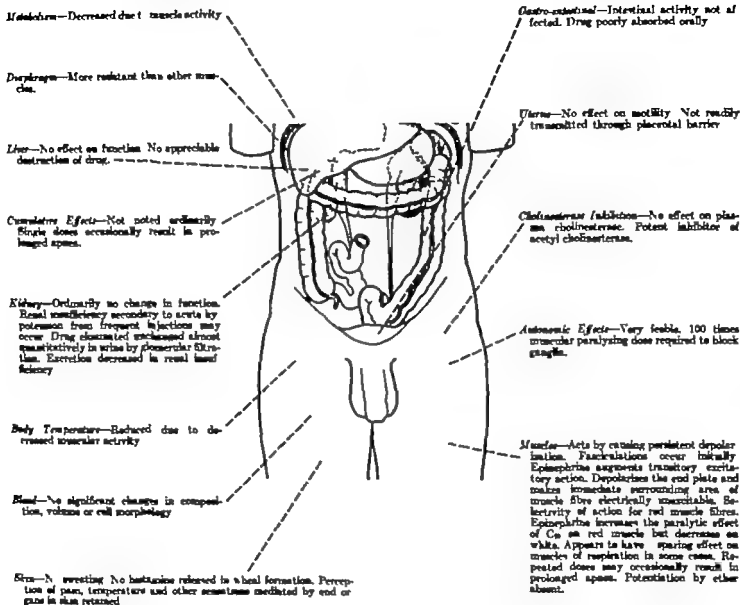
**Lungs**—No direct effect. Hyperventilation and apnea results from paralysis. Assisted or controlled respiration necessary.

**Heart**—No effect on myocardium. Does not influence arrhythmias. Does not sensitize automatic tissues. No effect on the circulation by paralyzing doses. Repeated or toxic doses may cause hypertension.

**Bronchi**—No direct effect. No significant amount of histamine released. Bronchospasm absent. Bronchial reflexes remain active. Spasm possible from local stimulation or irritation.

**Blood Pressure**—No appreciable changes with ordinary paralytic doses.





**ANTAGONISM**—Neostigmine and edrophonium of no value as antagonists. May enhance effect. Antagonizes depolarizing action. Small doses stimulate end plate of myasthenics.

**DOSE**—Initial dose of 2 to 3 mgm. at 1 mgm. per minute intravenously. On a weight basis four times more potent than d-tubocurarine. Onset of action same as d-tubocurarine. Duration of action is shorter. May cause tachyphylaxis.

## GALLAMINE (FLAXEDIL)

## SYNONYMS—Flaxedil, TRIEG

**HISTORY**—Synthesized and studied pharmacologically by Bovet and his associates in 1946 (Italy). Introduced into therapy by Huguenard (1949). First synthetic substitute for curare.

**CHEMISTRY**—A tri-quaternary base. Chemical name 1,2,3-triethyl amino ethoxy benzene. Available as a tri-iodide or tri-chloride salt. White, colorless, water-soluble, stable powder. Acid in reaction. Each cc. contains 20 mgm.

**Consciousness**—Not depressed. Electroencephalogram unaltered. Sedation remains clear in nonanesthetized patients.

**Eyes**—No effect on pupils. Lid relaxed. Extra-ocular muscles relaxed. No increase in intra-ocular tension.

**Intracranial Pressure**—No known effect.

**Tropheal Nerve**—Not affected. Sensation remains active.

**Temperature Regulating Center**—Not affected. Body temperature may fall due to decreased heat output from decreased muscle activity.

**Salivary Glands**—Continues to secrete. Quantity of not increased.

**Respiratory Center**—Ordinarily not affected. Massive doses may depress.

**Feeding Center**—No nausea or vomiting.

**Pharynx**—"Gag" reflex abolished due to loss of motor control of pharyngeal muscles. Secretions continue to flow and accumulate in the pharynx due to inability to swallow.

**Parasympathetic Center**—Not affected.

**Vagus Center**—Not affected. Exerts peripheral vagolytic action.

**Larynx**—Vocal cords relaxed. Summary of facts of larynx not affected in anesthetized subjects.

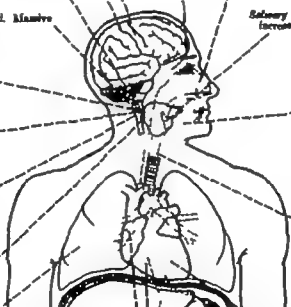
**Cough Center**—Not affected. Coughing inhibited due to paralysis of thoracic muscles.

**Lungs**—No effect. Hering-Breuer reflex remains active. Easier to inflate actively due to loss of resistance of thoracic muscles. Overdosage produces hyperinflation or apnea, requiring controlled or assisted respiration. Full use of muscle group not completely restored even when muscle tone appears normal.

**Heart**—No effect on myocardium. No disturbances in rhythm. Moderate sinus bradycardia results principally from weak but selective parasympatholytic action on the heart. Affords some protection against ventricular arrhythmias caused by epinephrine in combination cyclopropanes.

**Trachea**—No direct effect. Histamine release of no significance. Bronchial reflexes remain active. Spasms possible from local stimulation or irritants.

**Blood Pressure**—Not depressed, even by large doses.



**Metabolism**—Decreased due to decreased muscle activity

**Diaphragm**—More resistant than other muscle groups. Last to lose its activity and first to regain it.

**Liver**—No effect on function. Some destruction by the liver (less than 90%).

**Adrenal**—No known effect.

**Kidney**—No effect on renal function. Greater portion (75-100%) of an intravenous dose excreted into the urine within two hours. No histopathologic changes on renal parenchyma.

**Spinal Cord**—Synaptic transmission in the cerebrospinal axis unaffected.

**Bladder**—No known effect.

**Body Temperature**—Reduced due to decreased muscular activity. Elimination retarded by decrease in temperature due to decreased peripheral circulation.

**Autonomic Nervous System**—No significant effect on ganglia. Autonomic ganglia blocking activity negligible. Visceral structures innervated by autonomic nerves not significantly affected.

**Gastro-intestinal**—No appreciable effect on tone or motility. Not absorbed from gastro-intestinal tract.

**Uterus**—Motility not affected. Passes placental barrier to fetus.

**Muscles**—Acts competitively with acetylcholine at myoneural receptors. No fasciculation initially. Potentiated by other. Order of paralytic involvement of different muscle groups similar to tubocurarine.

**Blood**—No significant changes in composition, volume or cellular morphology.

**Skin**—No sweating. No histamine release (wheals). Perception of pain, temperature and other sensations mediated by end organs in skin remains active.

**ADMINISTRATION**—Onset immediate and maximal within four minutes given intravenously. The usual dose 1 mgm. per kilogram of body weight. Inactive orally. Absorbed subcutaneously in the muscles but slower. Cumulative effects result from repeated administration.

**POTENCY**—On a weight basis  $\frac{1}{3}$  as potent as d-tubocurarine. Duration of action is slightly shorter.

**ANTAGONISMS**—Prior dose prevents paralytic effect of decamethonium. Antagonized by anticholinesterases (neostigmine and edrophonium).

**MARGIN OF SAFETY**—Comparable to d-tubocurarine.



# NON ANESTHETIC DRUGS USED IN CONJUNCTION WITH ANESTHESIA

## 11 MUSCLE RELAXANTS

Curariforms	Myophenols	Quinine derivatives	Localizers	Huancarbutolins	Paralysants	Noncurariforms
Erythrosine	Tubocurarine	—	Localizers	Isobutyl	Neostigmine	Myoflexin
1 Studied by Tane in 1944	Studied by Burger and Brady 1946	Quinine and derivatives made by substituting alkyl radicals in nitrogen atoms of quinine have been studied. Made synthetically from quinine	Prepared by Taylor and Collier 1944. Lord by Robinson 1954	Prepared by Chaynal 1946	Synthesized by Boveri and associates. Used by Volkmann 1949	Studied by Ivin and Ar
Synthetic. Made from beta erythrosine found in erythrin plants	Synthetic	—	Synthetic	Synthetic	Synthetic	Synthetic
Dilute beta erythrosine	8 alpha tubocurarine-LB preparation	—	Essentially tubocurarine. Has blood materials.	6 carbon chain with two carbamate-choline groups at each end.	Same as neostigmine choline except one ethyl group replaces methyl on each nitrogen atom. Two quaternary	Hexamethyl (18 hexamethyl) disodium salt raised by 6 C
Contains one tertiary nitrogen atom	Contains no nitrogen atom	Quaternary base	Two quaternary nitrogen atoms separated by two carbons in chain. Stable solutions form methyl sulphate. pH 4.5	Two quaternary separated by two atoms.	—	Two quaternary raised by 6 C
Stable in alkali	Stable, but slightly soluble in H <sub>2</sub> O	Stable	Stable	Very stable. Hydrolyzed slowly	Form a di-alkali salt. Melts at 135°C.	Form a salt with alkali.
5-8 min.	5-8 min.	Flow onset. Not used	Flow onset. Not used	Slightly longer than neostigmine. 11-12 minutes	Slower to neostigmine choline 20-30 seconds	5-8 minutes.
Effective 1-10 mm. I.V.	10 min. 3 mm. I.V.	Quinine usually given several hours	Not observed. Response longer than to much of these tubocurarine	Not used. Lasts 1-6 hrs.	Not used. 1-15 minutes	Not effective. Relieved only during 1
30-60 min. Same as tubocurarine	2-7 min. I.V. Burns at intramuscular injection in spinal cord	—	Non-depolarizing. Also tubocurarine.	Non-depolarizing action	Depolarizing	Not known. Phosphoryl bromide with 1
Control depression with greater than curarizing dose	Depresses thalamus and cortex	None	None	None	None	None
Continues to form	Parasympathetic nervous system. Does not enhance	None	None	None	None	None
Causes hypotension	Larger doses depress R.A. Kala	None	None	None	None	None
None at curar	No known changes. Non-ordinarily. No nerve damage paralysis	No changes. Do not paralyze ordinarily	No changes. Does not completely relax curar	No changes. Appear	No changes. Like neostigmine choline	Acts with a base or other
Does not appear to have effect on sensory effect	No sensory effect. No sensory effect. May relax sensation	None. None. Slight	None. Flattened slowly. None. None	None. None. None	None. None. None	None. None. None
None	None	None. Not studied	Not present	None	Less than neostigmine choline	None. Less poor power. Acts as an ant. Not used
Antagonized	No effect	—	Antagonized by it	Antagonized by it	Not antagonized by	Only acts if there is a paralytic choline
No cumulative effect or tachyphylaxis	None	Some cumulative action	Cumulative effects	Cumulative	Not cumulative	Effective on oral curar but may be used
Antagonizes bradycardia. May be used	Very transient. Not suitable. May be used	Not useful. Quinine used for symptoms. May be used	Long lasting 1-8 hrs. May be used	Long lasting. 1-8 hrs. May be used	Shorter acting than neostigmine choline. May be used	None. None
Not known. Not known. Not known.	No significant effect. No significant effect. Indicated by exception by lower Part. Unmodified tubocurarine 0.1-1 gm. of a 6% orally	—	Less than d-tubocurarine. No significant effects	Less than tubocurarine. None	Indifferent. Indifferent. Hydrolyzed by plasma cholinesterase	None. None
20-75 mg. initial—100 average	10-15 mg. base and 0.5 mg. more potent than any tubocurarine	0.1-1 gm. of a 6% orally	75% potency of d-tubocurarine. Long lasting	At 20 mg. 100 mg.	20-40 mg.	10 mg. base. 1-2 mg. base. Low toxicity
No known effect. Preprecipitated by alkaline solutions	No known effect. Precipitated with alkaline solutions	Locally irritating. Precipitated by alkaline solutions	None. Preprecipitated by alkaline solutions	None	None. Not miscible with this point	None. Precipitated solutions



## ANTICURARE DRUGS (ANTICHOLINESTERASES)

Non-depolarizing relaxants antagonized by compounds which have (1) anticholinesterase effect or (2) have direct depolarizing action at myoneural junction. Anticholinesterases inhibit hydrolysis of acetyl choline and overcome curare effect by mass action. Anticholinesterases enhance effects of depolarizers (decamethonium). May reverse depolarizing effect of mixed block (phase II of block) by depolarizing agents. Anticholinesterases produce concomitant cholinergic effects in autonomic nervous system. Prevented by concomitant or prior administration of atropine.

Anticholinesterases may fail to re-establish block if (1) end plate receptors have lost affinity for acetyl choline, (2) pathological fixation of blocking agent at receptor (3) if an excess of acetyl choline forms which produces a depolarizing block of its own, (4) if prolonged depolarization of end plate by depolarizing drug is present.

Cholinesterase is an enzyme protein with 2 active sites—an anionic and an esteratic. Acetyl choline is bound at anionic site electrostatically. The carbonyl group binds at esteratic site to form an intermediate ester complex. This reacts with water and breaks up the ester linkage. Compounds like acetyl choline capable of producing quaternary ammonium ions, combine at the anionic site. They inhibit the enzyme competitively. Compounds with a carbonyl group (neostigmine a carbamate) combine at esteratic site to form ester type groupings. Acetyl choline forms at esteratic site to form readily hydrolyzable compound. Ester group formation with anticholinesterases, therefore compete with acetyl choline for place at esteratic site.

Chemically three principal types compounds exhibit anticholinesterases activity (1) alkyl and aryl carbamates (Neostigmine Pyridostigmine (Mestemon)) (2) quaternary ammonium ions (Edrophonium) (3) alkyl or aryl phosphates or fluorophosphates. These phosphates cause irreversible unions. Not suitable as anticurare agents.

Name	Edrophonium	Physostigmine	Neostigmine
Synonym	Tensilon	Eserine	Frostigmine
Source	Synthetic	Alkaloid from Calabar bean.	Synthetic
Chemical	A quaternary base 3, hydroxy phenyl dimethyl ammonium bromide. Has no carbamate acid grouping to attach to esteratic portion of cholinesterase.	Tertiary amine containing methyl or benzyl group attached to aromatic ring.	A trinitroethylated quaternary ammonium ion as well as a substituted carbamate acid ester, attached to both basic and esteratic grouping of cholinesterase.
Mechanism of Action	Weak anticholinesterase action. Is quaternary ammonium base which excites neuromuscular apparatus. Reestablishes transmission at neuromuscular junction by acting competitively with curare and displacing it from end plate. Enhances any existing depolarization.	Combines reversibly with cholinesterase. Onset of action gradual. Due to acetyl choline build-up.	Inhibits cholinesterase competitively. Reversible. Lasts 4-6 hours. Also has excitatory action on the neuromuscular apparatus. Massive doses cause some ganglionic blockade.
Distribution in Body	Does not penetrate epithelial or lipid barriers. Quaternary base—does not penetrate.	Penetrates lipid structures. Passes through epithelium.	Poorly absorbed—a quaternary base. Does not penetrate epithelial or lipid barriers.
Action on Skeletal Muscle	Competitive displacement of curare at end-plate. Reverses the action of curare. Fasciculations in large doses. Anticholinesterase activity of solitor consequences.	Causes fasciculations in large doses.	Reverses the action of curare and similar drugs. Fasciculations in large doses if used alone.
Central Effects	None. Does not penetrate into nervous tissues.	Intense increase in brain activity. E.E.G. pattern shows increased activity.	None. Does not penetrate into nervous tissues.
Autonomic Effects	Action similar to parasympathetic stimulation. Antagonized by atropine.	Manifests effects of parasympathetic stimulation by permitting accumulation of acetyl choline. Antagonized by atropine.	Manifests effects of parasympathetic stimulation. Antagonized by atropine.
Dose	5-10 mgm. I.V. Action transient. Reestablishment of displaced curare. 1 and plate may occur. Requires repeated doses. Action not cumulative.	Physostigmine Salicylate. Dose 0.5-1.0 mgm. Generally not suitable for severe over curarization.	Neostigmine Bromide tablets 15-30 mgm. Neostigmine methyl sulphate for I.V. use. Dose 0.5-1.0 mgm.

## THE PHARMACOLOGIC BEHAVIOR OF CHOLINERGIC (PARASYMPATHETIC) POSTGANGLIONIC AUTONOMIC FIBRES

**Ganglion**—Stimulated by nicotine at first, then depressed. Depressed by ganglionic blocking agents such as atropine and other alkyl substituted ammonium halides, benzthine and by direct application of local anesthetics.

**Pre-ganglionic Fibers**—Arise in cord and pass to autonomic ganglia. Nervous impulses arising in cord are transmitted to the ganglion which synapses with post-ganglionic fibre. Affected by direct application of local anesthetics.

**Tissue Enzymes**—A specific enzyme cholinesterase rapidly destroys the acetyl choline formed. Same as enzyme present at post-ganglionic nerve endings.

**Ending of Pre-ganglionic Axon**—Acetyl choline is released during nervous activity at this site. Stimulates dendrite of post-ganglionic fibre.

**Dendrite of Post-ganglionic Fibre**—Stimulated by acetyl choline thereby relaying the impulse from the pre-ganglionic fibre.

**Post-ganglionic Fibre**—Transmits impulses to organs. Blocked by direct application of local anesthetic drugs.

**Post-ganglionic Nerve End ing**—Acetyl choline is released by the impulse traveling down the fibre. Formation of acetyl choline not inhibited by parasympathetic depressants.

**Tissue Enzymes**—A specific enzyme present in serum or tissues, cholinesterase, hydrolyses acetyl choline into choline and acetic acid. Choline is approximately 1/1000 less active than acetyl choline. Hydrolysis is rapid and substance is quickly inactivated. Amount of acetyl choline liberated is minute—fractions of a milligram.

**Glandular or Muscular Structure**—May be inhibited by certain drugs—syntropin, trinitrophenol, papaverine etc or stimulated by barium, potassium, etc.

Physostigmine (serine) and prostigmine inhibit cholinesterase allowing a sustained action by acetyl choline on effector cells, resulting in prolonged parasympathetic stimulation.

D.F.P. (diisopropyl fluorophosphate) destroys enzyme. Hexa ethyl pyrophosphate yields prolonged inhibition but does not destroy enzyme.

**Receptor Substance**—Acetyl choline passes through junctional tissue and stimulates glandular or muscular structure. Threshold to acetyl choline elevated by benzthine, atropine, scopolamine, hyoscyamine, homatropine, neostigmine and other tropines. Parasympathetic depression results. Choline derivatives, methyl acetyl choline, carbamyl acetyl choline etc stimulate also. Parasympathetic stimulation results.



## ANTICURARE DRUGS (ANTICHOLINESTERASES)

Non-depolarizing relaxants antagonized by compounds which have (1) anticholinesterase effect or (2) have direct depolarizing action at myoneural junction. Anticholinesterases inhibit hydrolysis of acetyl choline and overcome curare effect by mass action. Anticholinesterases enhance effects of depolarizers (decamethonium). May reverse depolarizing effect of mixed block (phase II of block) by depolarizing agents. Anticholinesterases produce concomitant cholinergic effects in autonomic nervous system. Prevented by concomitant or prior administration of atropine.

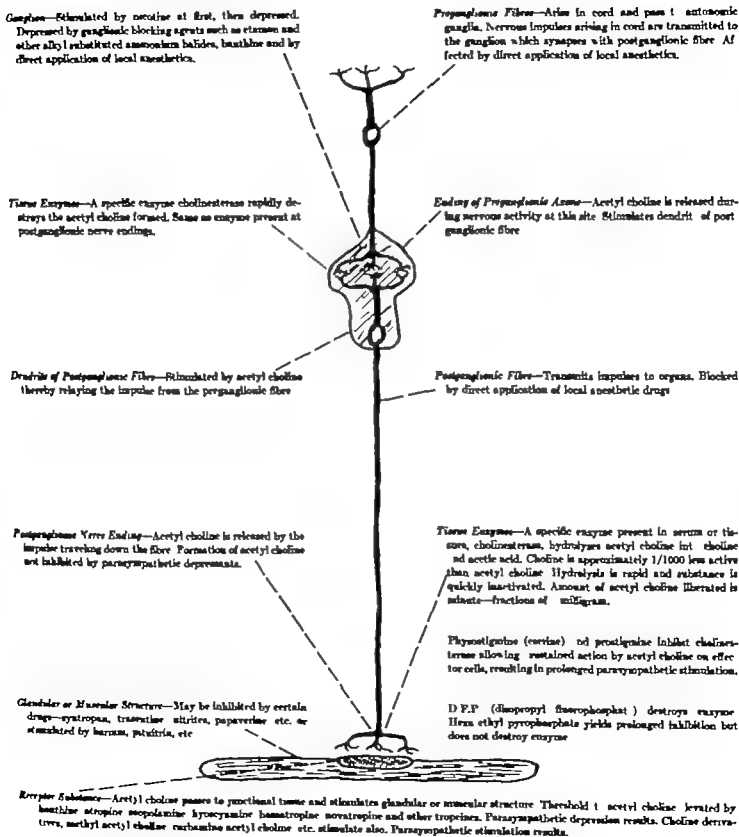
Anticholinesterases may fail to re-establish block if (1) end plate receptors have lost affinity for acetyl choline (2) pathological fixation of blocking agent at receptor (3) if an excess of acetyl choline forms which produces a depolarizing block of its own, (4) if prolonged depolarization of end plate by depolarizing drug is present.

Cholinesterase is an enzyme protein with 2 active sites—an anionic and an esteratic. Acetyl choline is bound at anionic site electrostatically. The carbonyl group binds at esteratic site to form an intermediate ester complex. This reacts with water and breaks up the ester linkage. Compounds like acetyl choline, capable of producing quaternary ammonium ions, combine at the anionic site. They inhibit the enzyme competitively. Compounds with a carbonyl group (neostigmine a carbamate) combine at esteratic site to form ester type groupings. Acetyl choline joins at esteratic site to form readily hydrolyzable compound. Ester group formation with anticholinesterases, therefore, competes with acetyl choline for place at esteratic site.

Chemically three principal types compounds exhibit anticholinesterases activity (1) alkyl and aryl carbamates (Neostigmine, Pyridostigmine (Mestinon)) (2) quaternary ammonium ions (Edrophonium) (3) alkyl or aryl phosphates or fluorophosphates. These phosphates cause irreversible unions. Not suitable as anticurare agents.

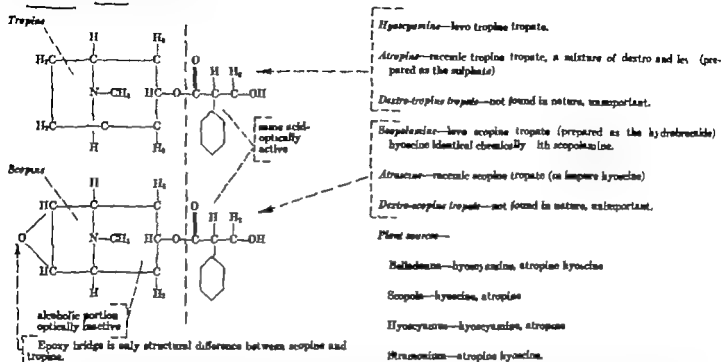
Name	Edrophonium	Physostigmine	Neostigmine
Synonyms	Tensilon	Eserine	Frostigmine
Source	Synthetic	Alkaloid from Calabar bean.	Synthetic
Chemical	A quaternary base, 3, hydroxy phenyl, dimethyl ammonium bromide. Has no carbamic acid grouping to attach to esteratic portion of cholinesterase.	Tertiary amine containing a methyl carbamic group attached to aromatic ring.	A trimethylated quaternary ammonium ion as well as a substituted carbamic acid ester attached to both anionic and esteratic grouping of cholinesterase.
Mechanism of Action	Feeble anticholinesterase action. Its quaternary ammonium base which crosses neuromuscular apparatus. Re-establishes transmission at neuromuscular junction by acting competitively with curare and displacing it from end plate. Enhances any existing depolarization.	Combines reversibly with cholinesterase. Onset of action gradual. Due to acetyl choline build-up.	Inhibits cholinesterase competitively. Reversible. Lasts 2-4 hours. Also has excitatory action on the neuromuscular apparatus. May even cause some ganglionic blockade.
Distribution in Body	Does not penetrate epithelial or lipid barriers. Quaternary base—does not penetrate.	Penetrates lipid structures. Passes through epithelium.	Poorly absorbed—a quaternary base. Does not penetrate epithelial or lipid barriers.
Action on Skeletal Muscle	Competitive displacement of curare at end-plate. Reverses the action of curare. Fasciculations in large doses. Anticholinesterase activity of saline consequence.	Causes fasciculations in large doses.	Reverses the action of curare and similar drugs. Fasciculations in large doses if used alone.
Central Effects	None. Does not penetrate into nervous tissues.	Intense increase in brain activity. E.E.G. pattern shows increased activity.	None. Does not penetrate into nervous tissues.
Autonomic Effects	Action similar to parasympathetic stimulation. Antagonized by atropine.	Manifests effects of parasympathetic stimulation by permitting accumulation of acetyl choline. Antagonized by atropine.	Manifests effects of parasympathetic stimulation. Antagonized by atropine.
Dose	4-10 mgm. I.V. Action transient. Reaccumulation of displaced curare at end plate may occur. Requires repeated doses. Action not cumulative.	Physostigmine Salicylate. Dose 0.5-2.0 mgm. Generally not suitable for severe over curarization.	Neostigmine Bromide tablets 15-30 mgm. Neostigmine methyl sulphate for I.V. use. Dose 0.5-1.5 mgm.

## THE PHARMACOLOGIC BEHAVIOR OF CHOLINERGIC (PARASYMPATHETIC) POSTGANGLIONIC AUTONOMIC FIBRES



## ATROPINE AND RELATED DRUGS

**CHEMISTRY**—All are alkaloids obtained from plants of order solanaceae. Structurally they are tropae acid esterified with tropine or scopine.



These alkaloids are basic in reaction in aqueous solution. They form salts with the mineral acids—sulphuric, hydrobromic, and hydrochloric. They are precipitated by the alkaloidal reagents. Hyoscyamine is converted to atropine by heat and alkali. Minute amounts possess marked activity. They possess two actions—a central one and a peripheral. Small doses (gr 1/150) stimulate the nervous system centrally and depress the myoneural endings of the parasympathetic division of the autonomic nervous system. Larger doses stimulate first and then depress.

## PARASYMPATHETIC DEPRESSANT DRUGS

Name	Chemical Name	Effect on Secretions	Effect on Cardiac Vagus	Effect on Gastro-Intestinal Tract	Effect on E.S.	Central Effect
Atropine	Tropine tropate.	Effective for anesthetic use.	Effective for anesthetic use.	Relaxes smooth muscle.	Causes prolonged mydriasis.	Stimulates.
Homatropine	Tropine mandelate (mandelic acid has one carbon less than tropic).	Weaker than atropine. Not suitable for anesthesia.	Less pronounced than atropine.	Less than atropine.	Causes less sustained effect.	Stimulates in large doses.
Homatropine	N methyl bromide of homatropine.	Weaker than homatropine.	Less than homatropine.	Is effective.	Less marked than homatropine.	Less marked than homatropine.
Eucatropine	N methyl sulfate of atropine.	Similar to atropine but less marked.	Similar to atropine but less marked.	Similar to atropine but less marked.	Similar to atropine but less marked.	Similar to atropine but less marked.
Eucatropine	Mandelic of papaverine base.	Much less than atropine. Not suitable for anesthesia.	Less than atropine.	Slight.	Unchanged for use in eye. Less intense than atropine.	Less than atropine.
Trametin	Diphenyl acetic acid ester of diethyl amine ethyl alcohol.	Slight.	Slight.	Prominent.	Slight.	Slight.
Pyridropine	Tropate of tertiary amine propyl alcohol.	Slight.	Slight.	Prominent.	Slight.	Slight.
Hyoscyamine	1 tropane tropate.	Similar to atropine.	Similar to atropine.	Similar to atropine.	Similar to atropine.	Similar to atropine.
Scopolamine	1 tropane tropate.	Similar to atropine.	Less than atropine.	Less than atropine.	Less than atropine.	Dampens reflex.

## ATROPINE

**HISTORY**—Recognized by Vauquelin in 1800 isolated and described as an alkaloid by Brandes in 1819

**Cerebrum**—Stimulated. Motor area more reactive to electric stimulation. Toxic doses cause excitement, convulsions or delirium.

**Temperature Regulating Center**—Stimulated by large doses. Blood center stimulated. Skin flushed and warm.

**Pain Center**—Slightly stimulated with therapeutic doses, resulting in slight blood pressure rise. Toxic doses depress and cause fall in pressure.

**Respiratory Center**—Stimulated. Toxic doses depress.

**Vagus Center**—Stimulated. Causes slowing the heart rate which persists until peripheral effect comes.

**Medullary Centers**—Stimulated. Degree depends upon dose.

**Central-nerve Cholinesterases**—No significant clinical effect.

**Lungs**—Respiratory rate slightly increased. Alveolar volume exchange increased. Tidal exchange increased. Relaxation of bronchial musculature from vagal depression. Oxygen consumption increased, carbon dioxide production increased, but total blood carbon dioxide unchanged.

**Metabolism**—Slightly increased.

**Gallbladder**—Bile production unaffected dose reduces. Reduces motility.

**Adrenal**—No change in epinephrine output.

**Liver**—Function not significantly changed. Carbohydrate metabolism unaffected.

**Kidney**—Not significantly affected by therapeutic doses.

**Cervix**—Relaxed. Movements inhibited. Relaxes spasms caused by morphine.

**Bladder**—Relaxed by large doses.

**Blood**—No significant changes. Bleeding and clotting time unchanged, slight increase in total leukocyte count.

**Elimination**—One therapeutic dose excreted within 14 or 15 hours. One-third, unchanged, found in urine. Remainder hydrolyzed; distributed in all tissues.

**Eyes**—Ends of parasympathetic nerves depressed, resulting in dilated pupil. Paralyzed ciliary muscle. Increase in intra-ocular tension, and decreased lacrimation also result. Action persists for several days.

**Mucous Membranes**—Secretions decreased. Drug absorbed from mucous surfaces.

**Larynx**—Laryngeal nerve depressed. Depresses vagus. Antagonizes spasm of nervous origin.

**Heart**—Biphasic action. Decrease in rate initially followed by increase depending upon dose. 1/100 grain gives slight decrease. 1st maximum preliminary decrease with 1/10 grain increase in rate due to paralysis of vagal endings. No effect on myocardium. Coronary blood flow increased.

**Blood Pressure**—No effect except in toxic doses.

**Autonomic Nervous System**—Depresses cholinergic autonomic fibers (postganglionic). Prevents muscarinic effects of acetylcholine and its esters. Blocking action on ganglia in larger than clinical doses.

**Stomach**—Motility emptying time and acidity not affected. Volume of secretion reduced.

**Intestines**—Motility emptying time and secretion decreased. Large doses needed to affect this response. Hypermotility reduced. Stimulated when hypomotility is present. Absorbed readily from mucous surface.

**Pancreas**—Secretions under vagal control diminished under hormonal control, unchanged.

**Uterus**—No effect. Slightly relaxed with large doses.

**Reflexes**—Cord stimulated by large doses; Babinski positive with large toxic doses.

**Skeletal Muscles**—Not significantly affected.

**Skin**—Insignificant local analgesic action.

**Body Temperature**—Increased due to increased metabolic rate and inhibition of sweating.

### ATROPINE STIMULATES CENTRALLY AND DEPRESSES AUTONOMIC NERVE ENDINGS PERIPHERALLY

**PROPERTIES AND PREPARATIONS**—An organic base. It is a white powder composed of crystals with an acrid bitter taste. It is poorly soluble in water (1 in 435). It forms salts with many acids, most important of which is the sulphate. The sulphate is a white odorless, granular powder inactive optically, melting at 190°C. and soluble in water (1 in 0.4 at 20°C.) alcohol and poorly soluble in chloroform and ether. Atropine sulphate is included in the U.S.P. XIII

## SCOPOLAMINE

**HISTORY**—Discovered by E. Schmidt in 1888

**Cortex**—Depression followed by drowsiness, and then a dreamless sleep. Hallucinations may precede sleep in some cases. Not an analgesic. Enhances hypnotic effect of morphine. Delirium follows use with pain.

**Temperature Regulating Center**—Not affected. Toxic doses may depress.

**Vasomotor Center**—Not affected. Large doses cause stimulation. Toxic doses depress.

**Respiratory Center**—Slightly stimulated. No depression. May antagonize depression of morphine. Toxic doses depress.

**Vagus Center**—Stimulated. May cause slowing of pulse.

**Vomiting Center**—Depressed. May overcome pain and nausea of central origin.

**Vagus**—Depressed at nerve endings. A less weakly than that of atropine.

**Lungs**—Tidal volumes reduced, rate increased, minute volume exchange increased. Bronchi relaxed.

**Metabolism**—Slightly reduced or no change.

**Adrenal**—No known significant change.

**Gallbladder**—Bile production unaffected. Smooth muscle or motility reduced. May relieve spasm.

**Liver**—No significant effect. Response similar to atropine.

**Kidney**—No significant effect.

**Uterus**—Relieves spasm similarly to atropine.

**Body Temperature**—No significant change.

**Autonomic Nervous System**—Depresses autonomic cholinergic nerve fibers.

**Eye**—Pupils dilate. Also causes loss of accommodation. Intra-ocular tension reduced. Qualitatively responses are more as atropine but quantitatively less intense.

**Larynx**—Vagal reflexes inhibited. Antagonizes spasm of nervous origin.

**Salivary Glands**—Depressed, more actively than by atropine. Action of shorter duration.

**Mucous Glands**—Secretions decreased. Drug readily absorbed from mucous surface.

**Heart**—Pulse unchanged or slowed. Toxic doses depress rate. No effect on myocardium.

**Blood Pressure**—No significant change. Toxic doses may depress.

**Gastrointestinal System**—Motility suppressed (vomiting and secretions reduced).

**Pancreas**—Secretions diminished.

**Uterus**—Stimulates contractions and relieves tone. Large doses depress.

**Nerves**—Not significantly affected.

**Skin**—No flushing or rash. Sweating inhibited.

**Blood**—No significant change.

**Reflexes**—Superficial and deep reflexes remain active. No significant change.

**Elimination**—Partly hydrolyzed by tissues.

**SCOPOLAMINE POSSESSES TWO IMPORTANT ACTIONS, A CENTRAL (ON CORTICAL DEPRESSANT ONE) AND A PERIPHERAL AUTONOMIC ONE (PARASYMPATHETIC DEPRESSANT)**

**PROPERTIES AND PREPARATIONS**—An organic base existing as an almost colorless, syrupy liquid. It crystallizes from an ether solution into a white powder which melts at 59°C. It is slightly soluble in water but soluble in alcohol, chloroform and ether. It forms salts with many mineral and organic acids, most important of which is the hydrobromide which is included in the U.S.P. XIII. The hydrobromide a white crystalline powder is bitter and slightly effervescent and dissolves in water (1 in 5) alcohol (1 in 20) but is insoluble in chloroform and ether.

## THE PHARMACOLOGIC BEHAVIOR OF ADRENERGIC (SYMPATHETIC) NERVE FIBRES

**Ganglion**—Stimulated by nicotine. Depressed by direct application of local anesthetic drugs, atropine, butylcholine and similar ganglion blocking agents.

**Preparasympathetic Fibers**—Arises from cord and transmits impulses from central nervous system.

**Tissue Enzyme**—Acetyl choline hydrolyzed by cholinesterase

**Preparasympathetic Nerve Ending**—Releases acetyl choline during nervous activity. Stimulates dendrite of postganglionic fibre

**Dendrite of Postganglionic Fibre**—(Stimulated by acetyl choline thereby relaying the impulse to the postganglionic nerve)

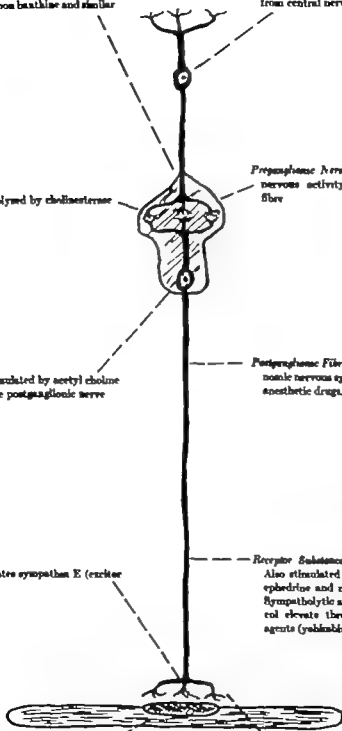
**Postganglionic Fibre**—Transmits majority of impulses in autonomic nervous system. Blocked by direct application of local anesthetic drugs.

**Postganglionic Nerve Ending**—Liberates sympathin E (exciter fibres) or I (inhibitor)

**Receptor Substance**—Stimulated by liberated sympathin E. Also stimulated by sympathomimetic amines (epinephrine, ephedrine and norepinephrine). Inhibited by sympathin I. Sympatholytic agents such as ergotamine, dibenzamine, prilocl elevate threshold to excitator substances. Adrenolytic agents (yohimbine) inhibit stimulating effect of epinephrine

**Gland or Muscle**—Acted upon directly by certain substances which stimulate epinephrine potentials, barium ion or by substances which inhibit, such as hexethine, nitrites, papaverine, etc

**Tissue Enzyme**—Epinephrine and other amines inactivated by oxidation or decarboxylation. No clearly defined inhibition of destructive agents such as occurs in parasympathetic system





## SYMPATHOMIMILE

Name	Euphrasine	Artazonal	Ephedrine	Dimethylphenylpropane	Metaphenylpropane
Stimulant	Adrenalin suprarenal	Not euphrasine Euphrasine	—	Metaphenylpropane Metaphenylpropane	Metaphenylpropane
Chemical name	Less methyl Amide attached	Euphrasine same methyl group on nitrogen	Has no hydroxyl group on aromatic nucleus. Has CH <sub>3</sub> group on $\beta$ carbon of amine	Ephedrine same OH on aromatic nucleus	Differ from ephedrine having only one hydroxyl group on aromatic nucleus
Comparison to other pressor drugs	Is standard of comparison	Lacks vasodilator component of euphrasine	Longer lasting than ephedrine	6 to 10 times more potent than ephedrine	Less potent. Longer lasting than ephedrine
Isomers	Optically active	Levo-isomer form used	Less ephedrine more active than dextro or racemic	Dextro-isomer is most potent and one used	Less isomer form is used
Properties	—	Bitartrate is white salt soluble in water	White crystalline substance prepared as sulphate or hydro- chloride	Hydrochloride is white crystal- line substance	White crystal in H <sub>2</sub> O
Stability	Unstable	Readily oxidized	More stable than hydrochloride is stable	Stable	More stable than ephedrine
Source	Mechanism of adrenal gland	Euphrasine from adrenal medulla contains 10%	From Ma Huang. Also synthet- ically	Synthetic	Synthetic
Destruction	Destroyed by oxidation	Oxidized rapidly by chromic acid	Steadily destroyed in blood	Steadily destroyed or eliminated	Oxidized
Effect on myocardium	Stimulates, increases output	No notable stimulating effect	Stimulates, increases output	Stimulates, increases output	Increases output
Effect on cardiac rhythm	Increases rate, stimulates myo- cardium	Increases output	Increases rate and output	Increases	Flows
Effect on arteries	Constricts some. Dilates others	Increases peripheral resistance all over	Constricts. Conspicuous effect	Increases	Constricts
Effect on venous	Dilates	Dilates	Dilates	Dilates	Dilates
Effect on venous	Dilates	Dilates	Dilates	Dilates	Dilates
Stimulation centrally	Causes tremor, restlessness	Less than euphrasine	Some central stimulating action	Passes through central stimulating effect	Slight stimulation or none
Effect on coronary	Dilates	Increases flow	Dilates and increases flow	Dilates	Dilates
Effect on veins	Constricts	Constricts	Constricts	Constricts	Constricts
Effect on peripheral arteries	Stimulates markedly	—	No effect	Same as ephedrine	—
Effect with cyclic propaganda	Causes ventricular fibrillation	Causes ventricular fibrillation	Causes arrhythmias of supra- ventricular origin	Same as ephedrine	Causes minor arrhythmias
Tachyphylaxis	None	None	Pronounced	Pronounced	Pronounced
Effect on venous pressure	Elevates markedly	Elevates	Elevates	Elevates	Elevates
Effect on diastolic pressure	Lowers 1 M. raises 1 V	Elevates	Slight elevation	Elevates	Elevates
Effect on pulse rate	Accelerates	Little change	Accelerates	Accelerates	Flows rapidly
Effect with epinephrine	Yes	No vasodilation	None	Like ephedrine	Reverses
Use in producing local anest.	Most effective of vasoconstrictors	More cases though	Not satisfactory	Not used	Moderate effect
Use in producing spinal anest.	Very effective	Equal	Not satisfactory	Not used	Moderate effect
Use in shock, massive hemorrhage	Effective	Equal	Satisfactory	May be used	1% effective
Use for therapy	Effective	Effective	Effective	Effective	Not so effective.
Onset of action Arterial L.V.	Immediate. Lasts several minutes	Transient like euphrasine	Within several minutes	Within several minutes. Lasts longer than ephedrine	0.2 mg raises B.P. for 10 min
Onset of action Arterial L.V.	Within 2-4 minutes. Lasts 2-10 minutes	Transient like euphrasine	30-60 minutes. Lasts several hours	Lasts longer than ephedrine	2 mg, raises B.P. 1-4 hrs.
Onset of action Arterial L.V.	Not effective	Not used	Effective. Lasts several hours	Effective. Lasts longer than ephedrine	30-60 mg raises B.P. 1-4 hrs.
Effect on respiration	Does not stimulate much. May cause apnea reflexly	None	Slight. Stimulating action on re- spiratory center	More central action than ephed- rine	Slight or none
Side actions	Tremor, muscular, pallor	Same as euphrasine	Tremor, muscular, pallor same	As vasopressor for spinal anes- thesia	Slight or none
Most common use	Vasopressor for spinal anest. Short action. Not suitable	As vasopressor	More prolonged than ephedrine same	More potent and longer lasting than ephedrine	As vasopressor, anal- gesic
Site of action	Adrenogen. Directly on effector cells	Adrenogen. Directly on effector cells	Adrenogen. Directly on effector cells	Adrenogen. Directly on effector cells	Adrenogen. Directly on cells

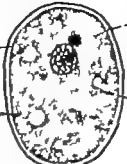
## DRUGS

Cocaine	Procaine	Prilvin	Clonase	Tamoxyl	Demethyl	Phlorin
Cardiac	Asphyxiates	Nephrotoxic	Cyclopropanol	Methocaine	E.A. I	Hypophosphine
2 (Lidocaine) mixed same propellant	Phenyl hex propylamine	N(1-Naphthyl methyl) methyl acetate	Cyclopropyl-4 methy- lamine propiate	Di methoxyl phenyl hex- propyl amine	4 methyl methoxyphenol	Contains phlorin (acetylene) and phlorin (naphthalene)
Delays from epinephrine is being about 1 in 100	More central than peripheral acting	Peripheral acting	Same potency as epine- phrine	—	Straight chain	Both are polyepinephrine of 8 amino acids.
—	Devoid from more active than or less	—	—	—	None	None
White powder	Base is soluble liquid. Salt is in white powder	Hydrochloride in white powder	Hydrochloride in white powder	Hydrochloride in white crystalline material	—	Biological product—dried plant. Also prepared arti- ficially
Not stable	Stable	Stable	Stable	Stable	Stable	Stable
Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Fast, loss of pituitary
Odorous	Resistant to sodium carbonate	—	—	—	—	Detected by liver
Base is epinephrine only has pituitary	Stimulates	Stimulates(?)	Stimulates	Does not stimulate	Stimulates	None. May reduce cardiac output (necrosis)
Lies epinephrine	Same ingredients in large doses	No serious anesthetic	No serious effect	No serious effect	Increases output	None
Constricts	Constricts	Constricts	Constricts	Constricts	Constricts	Constricts. Also constricts arteries
Dilates	Dilates	Dilates	Dilates	Dilates	Dilates	Constricts
Inhibits	Inhibits	—	Inhibits	Inhibits	Inhibits	Constricts
Less than epinephrine	Stimulates cardiac and respiratory	Little or none	1 less than epinephrine	Slight or none	None or slight	None
Dilates	Dilates	—	Dilates	Dilates	Dilates	Constricts, causes ischemia
Constricts	Constricts	Constricts	Constricts	Constricts	Constricts	Constricts
—	No effect	No effect	—	—	No effect	No effect
Causes arrhythmias	Same action as in irritability	—	—	Does not cause arrhythmias	No effect	Does not stimulate heart. Not like epinephrine
Prevent	Prevent	Prevent	Prevent	Prevent	Prevent	None
Elevates	Elevates	Elevates	Elevates	Elevates	Elevates	Elevates
Elevates	Elevates	Elevates	Elevates	Elevates	Elevates	Elevates
Increases	Variable. Usually reduces	Increases	Variable	Slows. Attempts reverse	Slight increase	Slows
—	Fails to reverse	—	—	—	—	None
1 less than epinephrine	Not used	Not used	Not as effective as epine- phrine	Not used	Not used	Not suitable
Not used	Not used	Not used	Not as effective as epine- phrine	Not used	Not used	Less effective than epine- phrine
May be used	Very effective	Used extensively	1% solution effective	Not used	Used	Not suitable
May be used	Not used	Not used	Used	Not used	Used	Not suitable
Within several minutes	1-4 mg. within 5 minutes	Not used	10 mg. for 10-15 min.	5-10 mg. for 10-20 min.	50-100 mg. 30 min.	Immediately 15-30 min.
—	Within 5 minutes 30 mg. for several hrs.	Not used	25 mg. for 30 min.	10 mg. 30-40 min.	100 mg. for 1 to 1 hr	5-10 min.
Not used	5-10 mg. for several hrs.	Not used	Not used	Not used	Not used	Not used
Lies but less than epine- phrine	Dilator stimulates	None	None	Does not stimulate	None	No effect
Lies epinephrine but not	Central stimulating effect	Slight or none	Lies epinephrine	Slight or none	Slight or none	Systemic from decreased out- put of heart
To produce local anes- thetics	T. reverse action. As an anesthetic	As counteranesthetic	As vasopressor as used during anesthesia	Vasopressor for spinal anesthesia	As vasopressor for spinal anesthesia	As vasopressor As oxytocin 4-10 min.
Advantage as anesthetic only	Advantage as anesthetic only	Advantage as receptor anesthetic	Advantage as receptor anesthetic	Advantage directly on effector cells	Advantage on receptor anesthetic	On all smooth muscle
—	—	—	—	—	—	Pituitary acts only on pregnant mammary
—	—	—	—	—	—	Pituitary on all muscle and

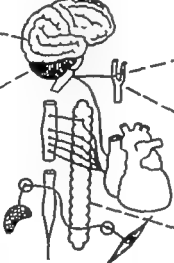
## ANALEPTICS

**DEFINITION**—An analeptic is a drug capable of stimulating the normal central nervous system which is used to overcome depression of that system. Ordinarily the term denotes restoratives used to reverse narcosis.

### BASIC MECHANISMS CAUSING ACUTE CENTRAL NERVOUS SYSTEM DEPRESSIONS


- 
1. Disturbances in cell nutrition resulting from changes in composition of arterial blood.
    - (a) Reduction in oxygen tension (anoxia) or carbon dioxide excess. Result of respiratory disease or failure.
    - (b) Reduction in concentration of nutritive material. Glucose is principal substance so affected.
  2. Disturbances in cell nutrition resulting from circulatory failure:
    - (1) All circulatory failure characterized by low systemic blood pressure acts accordingly—heart failure, shock, loss of vasomotor tone.
    - (b) Local circulatory changes—cerebral arterial spasm, thrombosis, increased intracranial pressure.
  3. Disturbance of intracellular metabolic processes:
    - (1) Depressant action of congenous substances—narcotic and hypnotic drugs.
    - (b) Action of exogenous substances—ketones and other products of disturbed metabolism.
    - (c) Disturbances of intracellular enzyme activity—deficiency diseases.

### TYPES OF ANALEPTICS

- 
1. Drugs whose value depends upon the stimulating action which is primarily or exclusively on vital centers in brain stem. Picrotoxin, cocaine, metrazol act primarily on medullary centers.
  2. Agents which act reflexly to stimulate vital centers.
    - (a) Carotid body stimulants—Lobelia, cyanides, nicotine act on the chemoreceptors to reflexly stimulate the medulla.
    - (b) Sensory nerve stimulants. Anesthetics, subcutaneous ether, camphor reflexly act on the nervous system.
    - (c) Physical agents—cold, sleeping, pressure on nerves, dilatation of sphincters reflexly stimulate the nervous system.
  3. Agents which improve blood supply to brain and restore the activity of vital centers by correcting the anoxia following circulatory failure. Usually cause hypertension and tachycardia—amyl, pituitrin, epinephrine.
  4. Agents which possess dual action and both stimulate the vital centers and the cardiovascular system. Benzadrine and decoryepinephrine possess vasoconstrictor and central action.
  5. Agents which affect cellular metabolism and affect respiratory enzyme action—pyruvates, succinates, fumarates and similar substrates may reverse narcosis in such a manner.

### POSSIBLE MODE OF ACTION OF ANALEPTICS

Exact mode of action of analeptics not settled. One or a combination of the following may explain mode and site of action:

- 
1. May inactivate narcotic by neutralizing effect—not probable.
  2. May cause decrease of concentration of narcotic in cell.
  3. May increase excitability of the nerve cell. Overcomes depression.
  4. May displace the narcotic from combination with dehydrogenases or may act as coenzyme. Affects respiratory enzymes.
  5. May combine with neural protoplasm to overcome effect of narcotic.

## CHIEF SITES OF ACTION OF ANALEPTICS

**CENTRAL NERVOUS SYSTEM**—Stimulants may act—(1) Selectively upon certain areas of cerebrospinal axis and ultimately stimulate all portions or (2) Act uniformly on all portions not favoring any particular portion (3) May stimulate from above downward (4) Stimulate from the cord upward Sustained intense stimulation is usually followed by depression. Not all stimulating drugs are suitable as analeptics. The suitable stimulants exert their primary action on the medullary centers.

**Cortex**—May be primary site of stimulation. Atropine camphor benzoin drive act primarily Metrazol, picrotoxin and strychnine act secondary after medulla has been stimulated. Overdosage causes convulsions. May be confined to only one group of muscles. Centers in cortex may be affected.

**Medullary Centers**—Drugs act by increasing blood flow through medulla or increasing sensitivity of cells to  $CO_2$ . Center needs  $O_2$  tension and is further depressed by  $O_2$  lack. Stimulating drugs of no value if depressed center without  $O_2$ . Center affected directly by picrotoxin, metrazol, camphor and atropine

**Vasomotor Center**—Stimulated usually after respiratory center

**Spinal Cord**—Stimulated in 2 ways

- (1) Briefly through somatic pathways. Rectal dilatation, subcutaneous ether or camphor inhalation of ammonia and irritating gases act reflexly
- (2) Directly on centers by specific drugs. Strychnine camphor and picrotoxin act this way. Tissue type of convulsions may result.

**Sympathetic Efferent Cells**—Frenor effect elicited by numerous anesthetics. Results in improved circulation in medulla and other structures affected by epinephrine, ephedrine, ephedrin, etc

**Peripheral Nerve**—Transmission of painful stimuli, cold, pressure, etc stimulate the centers reflexly

**Cerebral Body**—Cells respond to drugs which interfere with these respiration. The respiratory center is reflexly stimulated. Nicotine, lobeline, ephedrine and camphor exert primary action on chemoreceptor cells.

**Heart**—Cardiac output may be improved by dilatation of coronary vessels and subsequent increase in nutrition.

**Blood Vessels**—Vasoconstriction may follow stimulation of vasomotor center giving rise in blood pressure and increasing circulation.

**Smooth Muscle**—Stimulation causes vasoconstriction and improvement of circulation. Pituitrin and pituitrin so act.

**Combined Action, Muscle and Nerve Endings**—Certain sympathomimetic anesthetics act beyond as well as at effector cells, yieldingpressor action. Benzedrine, ephedrine and neosynephrine may so act.

**Muscle**—Stimulated directly by stretching. May reflexly stimulate respiration (tongue and pharyngeal muscles)

## DISADVANTAGES AND OBJECTIONS TO ANALEPTICS

- (1) They do not accelerate destruction or elimination of the depressant drug
- (2) A depressant action may follow stimulant action of analeptic and be superimposed upon depression from narcotic.
- (3) May increase oxygen consumption of cells already depressed by consistent anoxia.
- (4) Possessors undesirable side actions.
- (5) Convulsions may follow if inadvertently administered in mild depressions or in coma not due to depressant drugs.

## USES OF ANALEPTICS

- (1) To overcome depressed states, notably those resulting from narcosis.
- (2) To induce convulsions for various forms of "shock" therapy

## METRAZOL (CARDIAZOL)

**CHEMISTRY**—Metrazol is pentamethylenetetrazol. It is formed by condensing cyclohexanone with hydrazonic acid.

**PROPERTIES**

White crystalline powder M.P. 57 to 58°C. Soluble in water and most organic solvents. Aqueous solutions are neutral. Prepared in 10% aqueous solution for parenteral use. Used in tablet form (1.5 gr.) for oral use. Included in U.S.P. Stable and boils without decomposition.

**Muscle**—Stimulated when depressed. Onset of action and maximum effect immediate and brief.

**Respiratory Center**—Stimulated if depressed. No remarkable effect on normal center except with large doses.

**Vasomotor Center**—Stimulated by large doses administered rapidly causing an elevation of blood pressure. Suitable only in circulatory failure of central origin.

**Vagus Center**—Stimulated. May cause bradycardia.

**Vomiting Center**—May be stimulated causing nausea, retching and vomiting.

**Carotid Body**—No remarkable effect.

**Carotid Sinus**—No remarkable effect.

**Lungs**—Respiratory movement stimulated in both depth and rate. Metabolism increased.

**Elimination**—Distributed equally in all tissues. Rapidly detoxified in the liver. Cumulative dose detoxified in less than one hour. None detected in urine.

**Central Nervous System**—Stimulates all parts of the cerebrospinal axis. Stimulates from above downward.

**Cerebrum**—Stimulated. Marked restlessness, excitement and increased motor activity followed by epileptiform convulsions. Depression follows stimulation from large doses.

**Cerebral Vessels**—Dilated.

**Thalamus**—Stimulated. Convulsions occur after ablation of structures above thalamus.

**Card**—Stimulated by large doses. Restores depressed spinal reflexes. Increases hyperirritability resulting from strychnine and other card stimulants.

**Oral Mucosa**—Rapidly absorbed from (this site).

**Heart**—No stimulating effect on myocardium or conductive tissues. No effect on coronary vessels. Occasional transient premature beats.

**Blood Pressure**—Transient hypotension may follow from intravenous injection due to transient vasodilatation.

**Gastrointestinal Tract**—Readily absorbed from the gastrointestinal tract.

**Blood Vessels and Arteries**—No constriction. May cause dilatation of splanchnic vessels causing a transient hypotension.

**Arterioles (peripheral)**—No effect. Not suitable for peripheral circulatory failure.

**Capillaries**—No effect. Not suitable for peripheral circulatory failure.

**DOSE**

100-300 mgs. I.V.

**USES**

- (1) As stimulant in depressed states resulting from central nervous system depressants.
- (2) To reduce convulsions in shock therapy.

## Picrotoxin

**HISTORY**—Discovered by Boullay in 1819. First prepared in crystalline form by Pelletier and Couverbe in 1834

**CHEMISTRY**

Classed as an amaroïd (not an alkaloid). Contains no nitrogen. Structural formula undetermined. Empiric formula ( $C_{11}H_{12}O_6$ ). Probably composed of equimolecular portions of picrotin ( $C_{11}H_{12}O_6$ ) which is physiologically inactive and picrotoxinic acid ( $C_{11}H_{12}O_6$ ) which is convulsant.

**PREPARATION**

Extracted from the berries of *Cocculus indicus* and related plants indigenous to India and East Indian Islands. Berries used for trapping fish—fish berries.

**SYNONYMS**

Cocculus.

**Muscle**—Stimulated more prominently than other portions of cerebrospinal axis. Subconvulsive doses cause no effect in normal subjects.

**Respiratory Center**—Stimulated, particularly when depressed by narcotic drugs. Convulsive doses necessary to cause stimulation of respiration in normal subjects.

**Vasomotor Center**—May be stimulated, causing elevation of blood pressure. Subconvulsive doses cause no effect in normal subjects.

**Feeding Center**—Stimulated. Lungs occur frequently. Subconvulsive doses cause no effect in normal subjects.

**Vagus Center**—May be stimulated, causing slowing of heart. Subconvulsive doses cause no effect in normal subjects.

**Card**—Affected last. Reciprocal contraction not lost. Limbs are alternately flexed and extended.

**Erection**—Subconvulsive dose disappears from blood in 100 minutes. Traces may remain for several hours. All tissues take up drug. Detoxified in body—exact fate unknown.

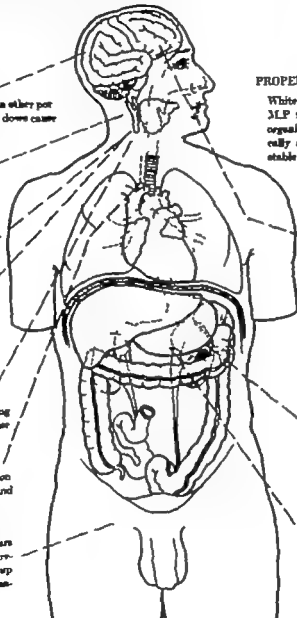
**PROPERTIES**

White intensely bitter tasteless, crystalline powder M.P. 300°C. Soluble 1 in 344 water at 10°. Soluble in organic solvents and alkalis. Aqueous solution optically active. Prepared in a 0.5% solution which is stable and neutral. Included in the U.S.P. XIII.

**Cortex**—Stimulates—less so at first than mid-brain or medulla. Large doses cause convulsions. Depression follows stimulation if convulsion occurs. Little or no effect in normal subjects until toxic doses are given.

**Absorption**—From all channels—oral, subcutaneous, intramuscular and intravenous.

**Stomach**—May be absorbed rapidly from mucous surface.

**USES**

For antagonizing barbiturate depression, particularly long and intermediate acting types. Also used for overcorrecting vertiginous narcosis.

**EFFECT OF ACTION**

Latent period lasting as long as 60 minutes. Action is sustained and prolonged. (Longer than strychnine)

**DOSE**

Packaged in 3 mgm. per cc. doses. Given slowly to secure desired therapeutic effect.

**CONTRAINDICATIONS**

Morphine poisoning. May enhance convulsions. Acute alcoholism.

## CORAMINE (NIKETHAMIDE)

**CHEMISTRY**—Coramine is the diethyl amide of nicotinic acid or pyridine  $\beta$  carboxylic acid. Effects on respiration noted by Faust in 1928.

**PROPERTIES**—Light viscous oily liquid, somewhat yellowish in color. Very soluble in water. B.P. 280°C.

**Cerebral and Aris**—Stimulates in large doses only. Toxic doses excite higher motor and other centers at first and then depress and cause death by respiratory failure.

**Vasomotor Center**—No direct effect. May affect it secondarily due to relief of anoxemia.

**Respiratory Center**—Stimulated reflexly via the aortic bodies. Affects a depressed respiratory center more than normal one.

**Cerebral and Aortic Body**—Partly reflexly stimulates respiration by stimulating chemoreceptors.

**Minerals**—Effective as vitamin in the case of pellagra and other diseases due to deficiency of nicotinic acid.

**Elimination**—No cumulative action. Rapidly inactivated. Presumably liver is site of destruction.

**Center**—Toxic doses stimulate and cause convulsions. These are followed by respiratory depression and coma.

**Lungs**—Increased ventilation if respiratory center is affected. Duration and degree varies with type of depression.

**Heart**—No notable effect. Elevation of blood pressure may follow use of large doses due to reversal of depression of vasomotor center.

**Blood Volume**—No significant clinical effect. Not suitable for respiratory depression due to shock. Not suitable for peripheral circulatory collapse due to blood loss, shock from trauma or collapse of neurogenic origin.

**Muscle**—Questionable increase in muscle tone with large doses. Not of clinical significance.

## PREPARATION

Sterile 2.5% aqueous solution. Coramine is proprietary name. Nikethamide is council accepted name.

## DOSE

0.250 to 0.800 gms intravenously or intramuscularly. Doses larger than 0.8 gms. should be administered very slowly and patient watched for signs of convulsions.

## USES

As an anesthetic in management of morphine, heroin or barbiturate and other types of central nervous system depression.

## BEMEGRIDE (MEGIMIDE)

## SYNONYMS—Megimide NP 15

**HISTORY**—First synthesized in 1911 during investigation of series of derivatives of glutarimide for anticonvulsive properties. Allied to glutethimide (Doriden) which is an alpha substituted glutarimide Marshall and Valence found alpha substituted compounds to be anti-convulsants. Studied pharmacologically by Shaw and his colleagues (Australia) 1951

**DESCRIPTION**—Chemically it is beta-ethyl methyl-glutarimide. White colorless compound with slightly bitter taste. Crystals irregular and hexagonal. Readily soluble in alkalis, alcohol, ether, acetone, benzene. Melts at 121°C. Aqueous solutions are neutral. Stable when autoclaved at 115°C. Crystallizes if stored in a cool place. Prepared in a saturated solution.

**Cerebrum**—Stimulated when depressed. Maximum peak effect obtained within 5-8 minutes. Duration variable, usually sustained.

**Respiratory Center**—Stimulated if depressed. No remarkable effect on normal center. Convulsions may appear before respiratory stimulation in non-narcotized patients.

**Vasomotor Center**—No appreciable effect in non-sensitive patients. May reverse hypotension due to depression by drugs.

**Vagus Center**—Not stimulated. Brady cardiac absent.

**Vomiting Center**—May be stimulated causing nausea, retching and vomiting if used in excessive doses.

**Cerebral Body**—No remarkable effect. Reflexes active.

**Cerebral Spines**—No remarkable effect. Reflexes active.

**Lungs**—Respiratory movements unopposed. Increase in minute volume exchange, rising both in depth and rate. Metabolism increased.

**Center**—Stimulated. Produces its effect in dosages below those which cause convulsions. Reverses the pattern of deep depression due to barbiturates and other hypnotics. Convulsions result if therapy is too vigorous. Exerts a cerebral stimulatory effect. Reverses hypoxic overdosage to the point of awakening. Excitement and restlessness on recovery. Does not displace barbiturate from receptor. Not a true antagonist.

**Heart**—No stimulating effect on myocardium or conductive tissues.

**Blood Pressure**—Tension usually normal. Hypertension may follow intravenous injection in lightly narcotized patients.

**Absorption**—Effective orally, subcutaneously or intravenously. Solubility in water 1-400. Used intravenously for most prompt effect.

## USES

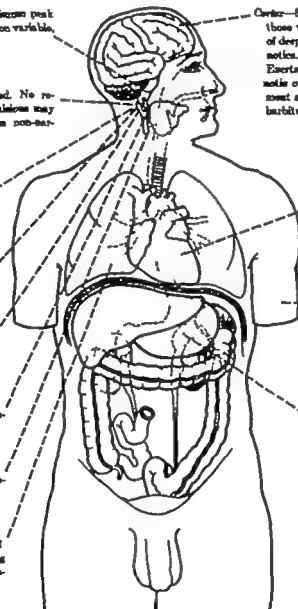
As an analeptic for depressed states resulting from overdosage of barbiturates and other hypnotics. Not true barbiturate antagonist. Evidence that it acts by competitive inhibition is lacking. Useful as an adjunct to essential supportive therapy.

## ADMINISTRATION

Intravenously in intermittent doses of 50 mgm. every 3 to 8 minutes until muscular tone increases and evidence of reflex activity appears. Maximum dosage varies with degree of depression. As little as 50 mgm. may be effective. As much as 600 or 700 mgm. may be required in markedly depressed states. Reversion may follow massive doses of hypnotics, particularly long-acting barbiturates.

## MARGIN OF SAFETY

Wider than with metrazol or picrotoxin. More effective than metrazol in treatment of coma.





## METHYLPHENIDATE (RITALIN)

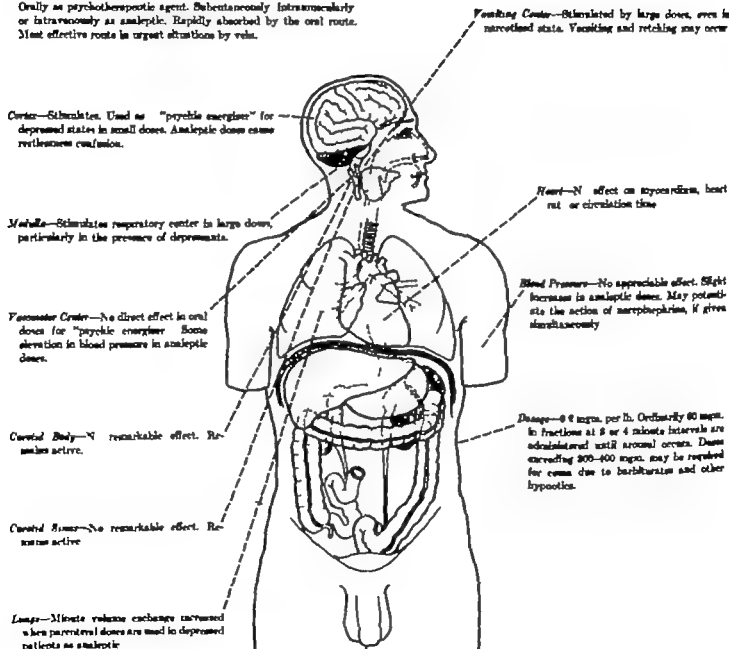
**DESCRIPTION**—Alpha phenyl  $\beta$ -piperidineacetate hydrochloride

**USES**

1. To alleviate drowsiness associated with antihistamines and tranquilizers.
2. As an analeptic to overcome depression from hypnotics
3. As a psychic energizer in depressed states (psychotherapeutic agent)

**ADMINISTRATION**

Orally as psychotherapeutic agent. Subcutaneously intramuscularly or intravenously as analeptic. Rapidly absorbed by the oral route. Most effective route in urgent situations by vein.



## ANALEPTICS OF LESSER IMPORTANCE

Name	Compound	Collector	Physiology C <sub>6</sub> H <sub>5</sub> N <sub>2</sub> O <sub>2</sub>	Alpha-Isobutyl	Sodium Succinate	Amphetamine
Pyrazol	4-methyl pyrazole			Label		Diphenol
Chemistry	Weakly-acidic or alkaline from pyrazole. A cyclic ketone not soluble chemically in water.	1,3,7-methyl xanthine. A stimulant from natural sources.	Alkaloid obtained from dried seed of <i>Physalis</i> very viscous. 0.2% solu- tion in water.	A derivative of pyrazole. Obtained from isobutyl alcohol. Label: isobutyl alcohol which contains three isobutyl, isobutyl, isobutyl, and isobutyl. Alpha is active.	Synthetic.	1,3-dimethyl, phenyl isobutyl. Synthetic. Forms hydrochloride salt. White, dry powder. Soluble, solu- ble in water. Potassium deposits slowly on stand- ing.
Preparation	Amorphous white sub- stance. Freely soluble in water. Soluble in organic solvents.	White, brown, crystals for oral use. (Caffeine) solu- ble in water. 1-15 solution for injection.	Red compound. Freely soluble. Soluble—77% al- cohol. Soluble—45% al- cohol. Soluble in water.	White powder. Making paste, 100°C. Liver- toxic. Freely hydro- chloride and sulphate which are used clinically.	White powder soluble in water.	Discard after 61 hours. Stable one week with re- frigeration.
Elimination	Excreted with glyco- cine and in liver and ex- creted into urine.	Excreted. Eliminated by diuresis. Some de- stroyed by body; some eliminated unchanged.	Destroyed by liver (con- sumed?) Small amount found in urine up to 5-6 days.		Metabolized in body.	
Primary Site of Action	Slightly stimulating to cardiac and vascular. Stimulates reflexly in arteriosclerosis hypotension. Concurrent in large dose.	Cardiac primarily. Large doses moderate, still larger doses spinal cord. Local subcutaneous or rectally in large doses.	Subal and primarily Metabolic after oral. Ac- cording stimulation.	Modest to slight extent. Cardiac body principally transient action. May induce gasp. Large doses depress the central nervous system.	Activation path of intra- ocular stimulation not de- pressed by narcosis as that of stimulus succinate injected.	Modest. Large doses act as convulsant. Not narcosis or barbiturate injected.
Effects on Circulation	No effects. Dilates cor- onary vessels. May affect blood pressure.	No effect on human heart. Blood pressure may rise moderately in central ef- fect.	No effect directly. Of no benefit.	Failure, then depression gasp. (See page 100) action. No benefit. No beneficial effect. Does not stimulate the heart or depress blood pressure.	None.	No remarkable effects. Not cardiac stimulant or vasopressor.
Effects on Respiration	No effect. Large doses may stimulate. Usually stimulates more later- ly.	May cause apnea increase. Not of benefit in marked depression.	No effect. Does which stimulates respiration more moderate the convulsant dose.	Minute volume exchange increased during several of gasp. May cause bron- choconstriction.	No remarkable effects. Respiratory depression.	Pulmonary. Increases mi- nute volume exchange by central stimulation.
Metabolism	No effect. Convulsant dose stimulates.	Slight increase in metabo- lism.	Increases by the convul- sant action.	Increased by large doses.	None.	Increased due to stimu- lation.
Other Central Effects	Stimulating from above threshold. Large doses cause gasp. Convulsant dose stimulates. Freely absorbed.	Large doses may affect metabolic. Mostly cor- tical stimulation.	Large doses produce cy- clic-like action. Convul- sant proved.	Action is on pharmaco- logy of cerebral body. In- creasingly marked by in- crease of gasp in the newborn.	None.	
Dose	0.1 gm. L.M.	0.2-1 gm.		0.2-0.5 gm. L.V.	0-6 gm. L.V.	
Remarks	Action variable. Not sol- uble in analgesic.	Action mild. Used to overcome "temporary ef- fects of hypoxia."	No tolerance develops. Of little benefit to analgesic.	Effective orally. Some general effects on res- piration only less potent.	Of doubtful value. Used to reverse barbiturate narcosis.	

# XIII. INORGANIC GASES USED IN CONJUNCTION WITH ANESTHESIA

## GASES AND VAPORS

**Molecular Composition**—Molecules of gases are composed of atoms. Some gaseous elements are monatomic (He—helium). Many are diatomic ( $N_2$ —nitrogen,  $O_2$ —oxygen,  $H_2$ —hydrogen,  $Cl_2$ —chlorine,  $Br_2$ —bromine) and others are triatomic ( $O_3$ —ozone). Non-chlorinated gases may be diatomic ( $NO$ —nitric oxide), tri ( $N_2O$ —nitrous oxide), tetra ( $NH_4$ —ammonia), penta ( $N_2O_5$ —nitrogen trioxide), etc.

**Pressure**—All gases exert pressure. Pressure is the force exerted by bombardment of the walls of a confining space by molecules. Force is exerted by rapid motion of molecules on side of containing space. Molecules tend to distribute themselves evenly in a given space (diffusion). *Traverse* (used in physiology) and *pressure* are synonymous.

**Boyle's Law**—The volume of a gas varies inversely as the pressure provided the temperature remains constant. Doubling the pressure halves the volume. Quadrupling the pressure reduces the volume to one-fourth. Reducing the pressure to one-half doubles the volume. To one-fourth quadruples the volume. Example: 100 cc. of a gas at 80° and 80 mm. Hg. will have a volume of 80 cc. at 400 mm. Hg. pressure.

**Charles' Law**—The volume of a gas varies in direct proportion to its absolute temperature if pressure remains constant. Volume increases 1/273 of its volume for each degree it is warmed above 0°C. and shrinks 1/273 of its volume for each degree it is cooled below 0°C. Example: A gas having a volume of 1 liter at 0°C. will have a volume of 8 liters at 873°C. provided pressure remains constant.

**Dalton's Law**—In a mixture of gases the pressure exerted by each gas is independent of the others and acts as though alone. The sum of the pressure of each equals total pressure. Example: In a mixture of 25% cyclopropane, 25% oxygen and 50% nitrogen having total pressure of 80 cm. Hg  $O_2$  exerts a pressure of 20 cm. Hg—cyclopropane 20 and nitrogen 40.

**Henry's Law**—The amount of a non-reacting gas which dissolves in liquid is directly proportional to the partial pressure of the gas provided the temperature remains constant. Solubility of gas decreases as the temperature rises or as the concentration of inorganic ions increases in the liquid. Example: If 1 gram of gas dissolves in a given volume of a liquid at 0°C. and 1 atmosphere, 2 grams will dissolve in 2 atmospheres, 4 grams at 4 atmospheres and 8 grams at 8 atmospheres. The solubility is independent of the pressure and remains constant for a given temperature.

**Graham's Law**—The rate of diffusion of one gas compared to another varies inversely as the square roots of their molecular weights. Example: Oxygen is 16 times heavier than hydrogen. It diffuses  $1/\sqrt{16}$  or  $1/4$  times as fast as hydrogen.

**Avogadro's Law**—Equal volumes of gases, even though dissimilar at standard conditions contain same number of molecules. One gram molecule of a gas or vapor equals 22.4 liters at standard conditions and contains  $6.06 \times 10^{23}$  molecules (Avogadro's number). The weight of dissimilar gases varies.

**Solubility Coefficients**—Ostwald's—The volume of gas absorbed by a unit volume of liquid at conditions of experiment. Between 0—1 volume of gas absorbed by unit volume of liquid 1 0°C. and 760 cm. Hg. pressure

**Critical Temperature**—Temperature to which a gas must be cooled to be liquefied by pressure.

**Critical Pressure**—The minimum pressure required to liquefy gas as it is cooled (at critical temperature)

**Standard Conditions**—The volume of a gas expressed at 760 cm. Hg. pressure 0°C. 22.4° Hg., or at 1033 gm. per sq. cm. or at 14.7 lbs. sq. in. at 0°C. or 32°F

**Vapor Pressure**—The pressure exerted by molecules escaping from liquid. When vapor pressure equals atmospheric pressure the liquid is at boiling point.

**Absolute Humidity**—Number of grams of water vapor per unit volume of gas at given temperature when there is complete saturation.

**Relative Humidity**—The amount of water vapor actually present in given volume of gas divided by the amount necessary for saturation at a given temperature times 100, expressed per cent. Example 100 cubic meters of gas hold 0.8 gm. of water vapor but can hold 1.0 gm. The per cent saturation is  $(0.8/1) \times 100$  or 80%.

## OXYGEN

**HISTORY**—First prepared by Stephen Hales in 1787 who did not recognize it as an element. Discovered by Priestley in 1771 also prepared by Scheele in 1771

**PREPARATION**

- 1 By the fractional distillation of liquid air. Nitrogen boils off first, oxygen remains as a liquid (most common method)
- 2 By heating  $\text{BaO}_2$  (barium peroxide). At  $800^\circ\text{C}$  forms  $\text{BaO}$  and  $\text{O}_2$ . At  $500^\circ\text{C}$ , red heat,  $\text{BaO}$  recombines with oxygen which is admitted into the furnace as air. Process is repeated



3. Electrolysis of water



- 4 By reacting water and sodium peroxide (ozone generator)

**PROPERTIES**

Clear, colorless, odorless gas. Molecular weight 32. Solubility 4.9 vols. in 100 cc.  $\text{H}_2\text{O}$  at  $0^\circ\text{C}$ . and 760 mm. Hg.; 3.1 cc. at  $60^\circ\text{C}$ .; 2.4 at  $80^\circ\text{C}$ . Specific gravity 1.103 (air equals 1). Liquifies at  $-118^\circ\text{C}$ . at 50 (micropressure pressure) boils at  $-183^\circ\text{C}$ .; solidifies at  $-218^\circ\text{C}$ . Electric sparks convert it to ozone ( $\text{O}_3$ ). Included in U.S.P. XIII fold as compressed gas in metal cylinders. Usually packaged at 6000 lbs. pressure. Standard color of cylinder given. Viscosity of gas at  $60^\circ\text{C}$ . 0.016 (water = 1)

**CONTENT IN BLOOD**

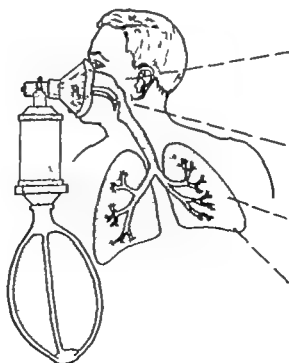
Released from hemoglobin by oxidizing agents (nitrites, ferrioxalate) with formation of methemoglobin, used in analytical methods. Approximately 10 cc.  $\text{O}_2$  may be released from 100 cc. blood normally

**REACTIVITY**

Supports combustion. Combines with hemoglobin to give oxyhemoglobin. One gram of hemoglobin combines with 1.34 cc.  $\text{O}_2$

**INFLAMMABILITY**

Forms explosive mixtures with oil and gases under high pressure in dispensing equipment. Will cause no reaction with non-combustible substances.



**Effect on Membranes**—Pure oxygen is an irritant if inhaled for period of 56 to 60 hours continuously causing pulmonary edema. Apnoeiform in animals irritated with 75% or more. Questionable decrease in secretions and increase in viscosity

**Effect on Cells**—Oxygen under pressure suppresses respiratory enzyme giving rise to oxygen poisoning.

**Diffuses**—Diffuses from isolated hole of lung rapidly. Rapid absorption may be factor in atelectasis in anesthetized with rich  $\text{O}_2$  mixture

**Effect of 100%  $\text{O}_2$** —Inhalation of pure oxygen increases dissolved blood oxygen four times. Has little effect on hemoglobin carried oxygen if no anoxemia exists. No increase in ventilation follows inhalation in non-anoxic subjects.

## INHALATION OF 100% OXYGEN

**Cerebral Activity**—Normal tonic control diminished. Apnea, referred to as oxygen apnea, results when 100% oxygen is given in acute anoxia (or a drug). Respiration is being maintained by the chemoreceptors by stimulus of anoxia. Removal of stimulus leaves center inactive. Apnea does not follow chronic anoxia when vagal reflexes are active and are maintaining respiratory drive.

**Metabolism**—Oxygen consumption not increased. Increased tension of no particular benefit. Normal rate do not utilize more oxygen than normal when higher tensions are inhaled.

At increased pressures 100% oxygen inhibits pyruvic oxidase and interferes with carbohydrate metabolism. Succinate dehydrogenase activity partly reduced. Total oxygen uptake of tissues decreased.

**Lungs**—After 2 minutes slightly depressed due to abolition of tonic chemoreceptor activity. Stimulation follows. M.V.E. increased 8% after 4-8 minutes. Pulmonary capillaries dilated. Irritant to lower respiratory passages. Subcutaneous edema follows continued inhalation of high oxygen tensions (over 280 mm. Hg).

**Lung Capacity**—Decreased after prolonged inhalation. Due to alterations in blood flow and pulmonary vasodilatation.

**Pulmonary Vessels**—Dilated by hyperoxygenation. Pressure increased. Constricted by anoxia; pressure decreased. Not related to changes in systemic pressure.

**CO<sub>2</sub> Transport**—M<sub>y</sub> interferes with CO<sub>2</sub> transport. Oxygen from plasma used up first. Less reduced hemoglobin available for CO<sub>2</sub> transport. At atmospheric pressures CO<sub>2</sub> elimination adequate. At 2.5 atmospheres body oxygen requirement is supplied by oxygen in plasma. No reduced hemoglobin available for CO<sub>2</sub> transport.

**Blood Concentration**—Saturation increased from 87.5 to 100%. Adds 0.8 volume % to hemoglobin transported oxygen. 17 vol. % added to 0.5% dissolved, raising total to 8 vol. %. Normally venous blood has 40 cc. Hg oxygen tension and 75% saturation. 100% oxygen increases it to 60 mm. Hg and 88% saturation. Arterial O<sub>2</sub> tension raised from 105 mm. to 600 mm. after 2 to 3 minutes. Pressure gradient for O<sub>2</sub> from blood to tissues markedly increased.

**Brain**—No cortical effects. E.E.G. unchanged. Cerebral vessels constricted. Cerebral blood flow decreased as much as 10%.

Confusion and disorientation follows relief of chronic anoxia due to CO<sub>2</sub> retention with subsequent toxicity due to acidosis. 100% O<sub>2</sub> under increased pressure, with few calories, causes nausea, vertigo, apprehension, depression leading to convulsions, epileptiform in character. Believed to be due to (1) inactivation of respiratory enzymes, (2) CO<sub>2</sub> retention.

**Eyes**—Retinal vessels constricted.

**Ears**—Eustachian tube obstructed after filling with 100% oxygen, is followed by absorption of gas and retraction of drum.

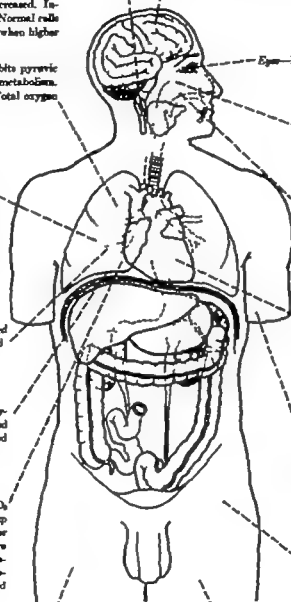
**Nose**—Obstruction after filling with 100% oxygen results in "vacuum headache" as O<sub>2</sub> is absorbed.

**Heart**—Decrease in pulse rate within 1-2 minutes of 3 or 4 beats per minute. Probably due to loss of chemoreceptor tone. Cardiac output reduced 10-25%. Stroke volume decreased. Coronary blood flow decreased up to 10%.

**Blood Pressure**—Slight increase in diastolic, no change in systolic. Due to increased peripheral resistance.

**Splenic Arteries and Capillaries**—Generalized vasoconstriction.

**Blood**—No apparent change in red blood count. Prolonged administration for several days suppresses formation of erythrocytes. Manifested by decrease of reticulocytes and not mature R.B.C. Had blood count not decreased due to long life of red cell. Newly formed (tagged with radioactive F) cells increase in number in circulating blood.



## CARBON DIOXIDE

Carbon dioxide is an inorganic gas of extreme stability formed by the complete oxidation of carbon

**HISTORY**—Isolated by Black in 1757

**PROPERTIES**—Colorless gas, possessing pungent odor and taste. M.W. 44 specific gravity 1.54 (air equals 1). Liquefies at 30.9°C. at 77 atmospheres. 50 atmospheres are necessary at 20°. Liquid is colorless; boils at -59°C. solidifies at -78°C. to -79°C.

**PREPARATION**

- (1) By the oxidation of coke and subsequent absorption of the gas by alkalis.
- (2) By heating alkaline earth carbonates.  $\text{CaCO}_3 \rightarrow \text{CaO} + \text{CO}_2 \uparrow$
- (3) As a by product from fermentation of sugars.

**Stability**—Highly stable (decomposes at 9000°C.) does not burn; acts as solvent for  $\text{O}_2$  in inflammable mixtures because it possesses a high capacity for heat. Absorbed by alkalis. Ba or Ca hydrides give a white precipitate. Present in atmosphere—.03% ionization in atmosphere may help dissipate electrical charges. Available as liquid in steel cylinders. Labeled grey at 75 or 10% with oxygen—grey green. Included in U.S.P. XIII. Liquefies under pressure at room temperatures. Viscosity of gas at 20°C. 0.015 (air=1)

**Solubility**—105 cc.  $\text{CO}_2$  dissolves in 100 cc.  $\text{H}_2\text{O}$  at 20°C. & 44 dissolves in 100 cc. at 37.5°C. Combines with water to form carbonic acid. Does not follow Henry's law

**USES**

1. For shock therapy for mental diseases.
2. To facilitate breakdown of carbon monoxide hemoglobin in CO poisoning.
3. To stimulate respiration (5 to 10% in pure  $\text{O}_2$ ) in depressed states and post-operatively.
4. As a quenching agent to reduce range of inflammability of explosive mixtures.
5. As an anesthetic in experimental animals.
6. To fluidify secretions in diseases of respiratory tract.

**DIFFUSION**

Diffuses from isolated lung lobule with occluded bronchioles in 6 minutes (air in 16 hours). Locally irritates skin.

**PHYSIOLOGICAL AND TOXIC EFFECTS****DEFINITION OF TERMS**

**Hypercapnia**—Increase in carbon dioxide tension of blood.

**Apnea**—Reduction of blood carbonates below accepted value

**Hypocapnia**—Reduction in carbon dioxide tension of blood below amount necessary to stimulate respiration.

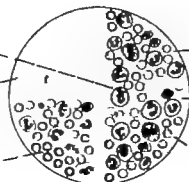
**Apnea**—Reduction of carbon dioxide blood tension below level sufficient to stimulate respiratory center

**BLOOD**

**Red Cells**—Increased in number in hypercapnia. No change in hypocapnia.

**Oxygen Content**—Free dissociation of oxyhemoglobin.

**Oxygen Capacity**—Unchanged.



**Clotting Time**—Shortened remarkably in hypercapnia. No change in apnea.

**Glucose**—Elevated. Due to glycogenolysis.

**Fatness**—Increased in hypercapnia. No change in apnea.

**Vasculi**—Pial vessels dilated; cerebral blood flow increased. Headache results after two hours of breathing 6% mixture.

**Intracranial Pressure**—Markedly elevated by concentrations over 8%.

**Vagus Center**—Stimulated by high concentration (after vasomotor center).

**Vasomotor Center**—Stimulated at first. Concentrations above 80% depress, causing fall in blood pressure. Blood pressure rise persists under halothane anesthesia.

**Vomiting Center**—None.

**Respiratory Center**—Diffuses readily into and stimulates center. Depressant drugs raise threshold to it so that it is unaffected in drug overdose.

**Cerebral Body**—Stimulated by tensions above those which stimulate respiratory center; therefore influences respiration little at this point.

**Lungs**—Increase in alveoli of 0.1% doubles ventilation; decrease of 0.1% causes apnea. 1 to 8% in inspired air increases tidal volume 3 to 4% (increase rate as well as tidal volume 8.0% to 10.0%); air increases ventilation 80% to 89%, 16.4% causes decrease in ventilation to 185% and severe dyspnea with higher concentrations; mucous secretions supervene.

**Bronchi**—Constricted by low concentration; dilated by high.

**Metabolism**—Oxipent 800 cc. per minute average. Varies with metabolic rate. Concentration of various parts: pharynx 8% to 8%, lips 2.5% to 4.0%—with mask on subject during ventilation.

**Diaphragm**—Stimulation of phrenic nerves via respiratory center increases ventilation.

**Liver**—Glycogen mobilized during hypercapnia. Hyperglycemia results.

**Kidney**—Carbonated steam may promote diuresis.

**Apnea During Anesthesia**—Hyperventilation, 10 to 15 minutes, changes pH from 7.35 to 7.70;  $CO_2$  tension from 40 mm. to 0 mm.—total  $CO_2$  halved; heart unchanged; blood pressure dropped 80 to 90 mm. systolic and 10 to 20 mm. diastolic; apnea 8 to 10 minutes after no shock; recovery complete; hypotension not progressive; returns to normal during ventilation.

**Cornea**—No effect until large concentrations are inhaled. Slight stimulation followed by depression causes narcotic effect. Small animals anesthetized with 80% or more (with  $O_2$ ); 90% to 95% anesthetized dogs in 1 minute. Reflexes disappear; muscles relax, twitching. Convulsions occur in man after 10 to 15 minutes. Anesthesia may be prolonged for two hours in animals. Asepsia causes dullness and mental apathy.

**Mucous Membrane**—Irritated by low concentrations causing pungent sensation. Stimulation of watery secretions from mucous glands (100%).

**Pharynx**—No effect ordinarily. Large concentrations cause spasm.

**Larynx**—No effect ordinarily. Large concentrations cause spasm.

**Heart**—Cardiac output increased by moderate amounts—6% or more. Junctional tissues increase in sensitivity if pH is lowered, resulting in arrhythmias. Little affected by asepsia.

**Venous Pressure**—Increased due to dilatation of peripheral vessels.

**Blood Pressure**—Elevated. Falls, sometimes to below base level, when gas is withdrawn.

**Blood Vessels**—May constrict. Peripheral vessels dilate. Diastolic pressure may fall due to decreased peripheral resistance.

**Gastrointestinal Tract**—Hyperemia of mucosa facilitates absorption. Increases secretion of gastric juices. Some gas absorbed from mucous membrane.

**Muscles**—No effect ordinarily. May influence maintenance of tone. Tone decreased in hypoxemia. Retard when asphyxia is induced.

**Skin**—Mild irritant to skin. Skin vessels dilated. Temperature rises.

**Chlorine Tendency**—None.

**Hyperapnea During Anesthesia**—Respiratory rate increased, followed by depression; blood pressure elevated as in non-anesthetized subject. Pulse slightly altered; further addition of  $CO_2$  depression does not alter respiratory rate.

## HELIUM AND RARE GASES

**HISTORY**—Belongs to a group of chemically inert gases known as the rare gases. Noted in the spectrum of the sun by Lockyer and Edén in 1867. Isolated in 1895 by Ramsay. Occurs in the atmosphere 1 part to 85,000. Chief world source is natural gas of oil wells of southwest U. S. which contain up to 2% of element. Separated from other gases by compression. All other gases liquify before the helium. Clinical use reported by Barach in 1936 in New York.

**PROPERTIES**

Colorless, tasteless, odorless gas. The second lightest gas known. Molecular weight and atomic weight, 4.0. Specific gravity 0.1785 (air equals 1). An inert, monatomic element. Boils at  $-268^{\circ}\text{C}$ . at 2.0 atmospheres pressure. Solidifies at  $-272^{\circ}\text{C}$ , boils at  $-273^{\circ}\text{C}$ . Not absorbed by activated charcoal even at low temperatures. Diffuses through some solids including glass. Possesses a high rate of heat conductivity. Viscosity at  $0^{\circ}\text{C}$  0.010 (water=1).

**Specific gravity of mixtures as follows**

75% He—41%  $\text{O}_2$ —3.41 (air equals 1)  
85% He—25%  $\text{O}_2$ —1.9% (air equals 1)

**Depressant Action**—Obeys Overton-Meyer law. Possesses low oil sol. Causes no depression at atmospheric pressure. No depressant effect under increased pressure in diving bells. (Nitrogen does.)

**Effect on Membranes**—None. May cause small loss to voice due to lightness and effect on sound waves. No effect on nerves.

**Toxicity**—Physiologically as well as chemically inert. It undergoes no change in tissues. Combines with nothing. Exerts no anesthetic action in cells and body fluids. Displaces nitrogen in tissues and body fluids. Not absorbed over a period of hours. Causes death by asphyxiation if insufficient oxygen is inhaled.

**USES**

- (1) To facilitate respiratory exchange in acute and chronic obstructions of respiratory tract (asthma, tracheitis, bronchitis, etc.).
- (2) As a speaking agent for reducing range of euphonia of anesthetic mixtures.
- (3) As a diluent to replace nitrogen air for deep sea diving.
- (4) As a contrast medium instead of air in cinematography and similar procedures.
- (5) As a diluent (or oxygen) in inhalation anesthesia (to avoid high oxygen concentration).

**Solubility**—In  $\text{H}_2\text{O}$ , at  $0^{\circ}\text{C}$ , 0.0 vols.  $\text{O}_2$ —most insoluble of gases

1  $\text{H}_2\text{O}$ , 0.07 at  $37^{\circ}\text{C}$ ,  
in oil, 1.48 at  $37^{\circ}\text{C}$ .  
Oil-water ratio, 17

**Storage**—Marketed as a compressed gas in steel cylinders. Bureau of Standards color—brown with oxygen, green and brown. Included in the U.S.P. VIII.

**Utility**—Not essential in III. Used because of lightness and great diffusibility. Decreases resistance to breathing.

**Elimination**—Not altered in body. Minute amounts pass through skin. Most is eliminated through lungs. Elimination slow—requires several hours, if tissues have been saturated.

**Absorption**—Complete body saturation requires 8 to 7 hrs. Diffuses slowly from isolated lobes of lung with circulation intact (10 hours air in 10 hours).

**Effect on Circulation**—Lightens respiratory load and decreases effort in breathing.

**METHOD OF ADMINISTRATION**

- (1) By semi-closed method continuous (expensive and wasteful)
- (2) By semi-closed method followed by closed system.
- (3) In closed hood with rebreathing

**OTHER RARE GASES**—Neon, argon, xenon, krypton are also inactive and inert elements. Argon behaves like nitrogen when inhaled under pressure and causes nervous system depression. It possesses a higher oil-water ratio than helium. Oil-water ratio 3.32. Other gases have not been used clinically. The rare gases are inert and possess no valence are essential to life. Surgical anesthesia has been produced by the inhalation of xenon.



## NITROGEN

**HISTORY**—Nitrogen is an inert diatomic element which combines with other elements with difficulty. First isolated by Rutherford in 1782.

**PREPARATION**

1. By the fractional distillation of liquid air as a by-product in the manufacture of oxygen.
2. By heating ammonium nitrite in air (laboratory method)  $\text{NH}_4\text{NO}_2 + \text{Heat} \rightarrow \text{N}_2 + 2\text{H}_2\text{O}$
3. By absorbing oxygen from air by suitable chemical. Residual gas is nitrogen.

**PROPERTIES**

Colorless, inert, tasteless gas. Molecular weight 28 specific gravity 0.947 (air equals 1) Solubility 2.4 cc. at 0°C. and 76 cm. Hg. 1.28 vols. % dissolve in  $\text{H}_2\text{O}$  at 37°C.; 0.87 vols. % in oil. Oil/water ratio 2.2:1. Liquefies at  $-140^\circ\text{C}$ . 1.75 atmospheres pressure. Solidifies at  $-214^\circ\text{C}$ . Boils at  $-186^\circ\text{C}$ . Does not combine with water or other substances. Aided by high pressure and electricity it forms oxides,  $\text{NH}_3$  etc. Does not support combustion. Dispensed as a compressed gas in steel cylinders. Critical temperature below room temperature. Possesses a high heat capacity and is, therefore, an effective quenching agent. Viscosity of gas at 30°C. 0.017 (water=1)

**USES**

- (1) As diluent to reduce high oxygen tensions during inhalation anesthetics.
- (2) As quenching agent in anesthetic mixtures to reduce range of inflammability.
- (3) To induce anesthesia for diagnostic purposes (cardiac disease) or therapeutic purposes (shock therapy in mental disease).

**EFFECT ON TISSUES**

No known effect. Causes death from asphyxia if administered pure

**NARCOTIC ACTION**

Obeys Overton-Meyer Law. No narcotic action ordinarily. Possesses narcotic properties when administered at several atmospheres pressure. Causes central nervous system depression in divers. Rapid decompression causes appearance of bubbles in tissues and syndrome known as "the bends".



**Diffusion**—Elimination from tissues follows physical and chemical laws pertaining to other inert gases. Pains from isolated lung lobes with blood supply intact in 18 hours (air requires 10)

**Absorber Concentration**—Tension in mm. Hg: 578 alveolar; 880 inspired; 578 expired.

**Distribution in Tissues**—Does not combine in body. Exists in simple solution in plasma inter and intra cellular fluid. Arterial and venous blood concentration identical. Dissolved in all tissues and body fluids. Found in hollow viscera such as pleura, intestines. Displaced slowly by oxygen or helium using semiclosed apparatus. Mix to seven hours required for almost complete desaturation.

## XENON

**HISTORY**—Discovered by Ramsay and Travers (1898) in liquid air. Lawrence (1940) suggested from work in rats and oil/water ratio that Xenon should have anesthetic properties. Introduced as an anesthetic agent in animals and man by Cullen and Gross in 1952 (Iowa). Pittinger and co-workers studied pharmacologic properties.

**PROPERTIES**—Rarest and heaviest of the rare gases. Xenon ( $Xe$ ) is a colorless, odorless, tasteless, non-irritating inorganic gas. Present in the atmosphere in a ratio of 1 to 20 million of air. Obtained as a by-product of the fractional distillation of liquid air. Inert. Forms no stable compounds with other elements. MW 131.3 A.W. 151.3 B.P.  $-107.1^{\circ}C$ . M.P.  $-118^{\circ}C$ . Density 5 gm per liter. Critical temperature  $14.8^{\circ}C$  at 87 atmospheres. Slightly more viscous than air.

**Absorption Coefficient**—1.7 in oil at  $57^{\circ}$  and .588 at  $87^{\circ}$  in air. Oil/water ratio 40.

**Concentration**—80%–90%. Yield anesthesia lower 1st plane upper end plane.

**Electroencephalogram**—Difficult to differentiate definite levels. Patterns consisting of burst suppression and total suppression not seen, even at maximal concentrations. Frequency is slowed but is more rapid than that noted with ether or cyclopropane. Does not produce very slow single rhythmic pattern of type seen with ether. Change is not as marked or dramatic as those described for other agents.

**Potency**—Comparable to that of ethylene.

**Eyes**—Lid reflex disappears. Corneal reflex active.

Rolling eyeballs. Pupils constricted. Lid reflex absent.

**Salivary Glands**—No mucous formation.

**Pharynx**—Reflex obtunded. Airway tolerated during anesthesia.

**Larynx**—No spasm, no irritation, no mucous formation.

**Heart**—Relative bradycardia occurs. Blood pressure remains unchanged. Arrhythmias absent.

**Muscles**—Sufficient relaxation of jaw muscles to insert airway. Neuromuscular activity (twitches and convulsions) absent.

**Distribution in Tissues**—If quantity in brain = 100%, radioactive Xenon is distributed as follows: In other tissues Adrenal gland 18%; liver and spleen 59%; striated muscle 65%; perirenal fat 100%; heart and thyroid 90%; skin 81%; fat deposits 85%. Bone, urine—traces. Stable in body. Eliminated by exhalation.

**Blood Oxidation**—80–90 mixture does not inhibit guinea pig brain tissue oxidation.

**Medullary Centers**—No apparent depression or stimulation.

**Lungs**—Respiration not altered appreciably. Ventilation adequate. Not irritating.

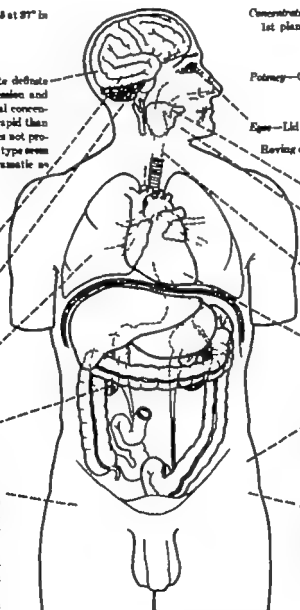
**Kidney**—Urea clearance unchanged.

**Blood**—Hemoglobin content, red and white cell, hematocrit per cent, sedimentation rate, bleeding and clotting time unchanged. Relative increase in the number of segmental cells.

**Crustal ions**, non-protein nitrogen, phosphorus, potassium, sodium, urea nitrogen unchanged. Glucose slightly decreased. Right increase in platelets. N increase in urine. Right decrease in serum potassium. Relative bradycardia.

**Flammability**—Completely inert, non-explosive. Molecule has no binding force.

**Cost**—As research tool only. Expensive and scarce.



## ADMINISTRATION

Reinforced system during induction: closed for maintenance.

(a) Consciousness—Lost at 80% inhaled concentration.

(b) Induction—Rapid, mild without excitement.

(c) Recovery—Rapid—within 5 minutes. No excitement. Consciousness clear.

# SECTION XIV SOME CLINICAL CONSIDERATIONS

## PRE-ANESTHETIC MEDICATION

Reasons for administering premedication and drugs used are as follows:

- (1) For psychic sedation—barbiturates, opium alkaloids, avertin.
- (2) To obtain an additive or synergistic effect—(opium alkaloids, demoral, procaine, methadon) between drugs and contemplated anesthetic agent.
- (3) To reduce reflex irritability and metabolic rate—opium alkaloids, avertin.
- (4) To suppress secretions—atropine, scopolamine.
- (5) Prophylactically to overcome undesirable anticipated side effects caused by the anesthetic agent.

**Nervous System**—Psychic sedation causes depression of cortex and calms patient. Analgesic drugs suppress pain and decrease reflex irritability. Second stage shortened when patients are sedated. Drugs depressing cortex, midbrain and other centers antagonize stimulating action of local anesthetics.

**Respiratory System**—Depressant drugs decrease  $O_2$  consumption. Induction and maintenance of anesthesia with agents requiring high partial pressure are facilitated by this response.

**Breaths**—Vagal reflexes from stimulation locally or manipulation of larynx inhibited.

**Metabolism**—Reduced by central nervous system depressant. Dosage of premedicating drug must be adjusted to following factors:

- (a) **Age**—Metabolic rate decreases with age. Less premedicating agent necessary. Metabolic rate highest in infancy.
- (b) **Sex**—Variation in metabolic rate between sexes of minor significance. Rate increased at puberty.
- (c) **Fever**—Increases metabolic rate markedly (7 calories per degree F). Dosage may be increased.
- (d) **Pain**—Increases metabolic rate. More premedicating agent required.

**Disorders of Metabolism**—Thyrotoxicosis necessitates increased dosage of premedicating agent. Hypothyroidism requires decreased dosage. Cachexia reduces metabolic rate profoundly.

**Mucous Secretions**—Parasympathetic depressants (atropine, scopolamine) inhibit salivary and mucous secretions.

**Larynx**—Spasm of central origin inhibited by parasympathetic depressant (atropine).

**Circulatory System**—Blood pressure and pulse approach normal due to release of psychic influence.

**Prophylaxis**—Parasympathetic drugs (atropine) given to counteract vagal stimulation. Drugs exerting procaine action given in anticipation of circulatory failure (epidural or spinal anesthesia).

**Mesenteric Reflexes**—Traction on visceral structures inhibits circulatory and respiratory disturbances. Inhibited by atropine.

## METHOD FOR VARIOUS TYPES OF ANESTHESIA

**Inhalation Anesthesia**—For adults of average size with normal metabolic rate use morphine gr.  $\frac{1}{2}$  atropine or scopolamine gr.  $\frac{1}{100}$  intramuscularly one and one half hours prior to induction of anesthesia. May be administered intravenously 10 minutes prior to anesthesia. Dilaudid gr.  $\frac{1}{30}$ , demoral  $\frac{1}{15}$  or methadon gr.  $\frac{1}{2}$  may be substituted. Decrease dose as age increases or if metabolic rate is reduced.

**Regional Anesthesia**—For adults of average size morphine gr.  $\frac{1}{2}$  and scopolamine gr.  $\frac{1}{100}$  intramuscularly supplemented by a therapeutic dose of a short acting barbiturate such as pentobarbital or avertin. For spinal anesthesia the barbiturate is omitted.

**For Intravenous Anesthesia**—Morphine and scopolamine or atropine in the same manner as for inhalation anesthesia.

**For Psychically Disturbed or Extremely Anxious Patients**—Basal narcosis with avertin, etal or intravenous pentothal or etal or paraldehyde may be used.

**For Subjects Intolerant to Morphine**—Dilaudid, demoral, methadon or pontaron may be used.

## MORPHINE-ATROPINE

Morphine and atropine in the ratio of 25 parts to 1 respectively administered intravenously 10 minutes prior to anesthesia or subcutaneously one and one half hours prior to anesthesia produces the following effects

**Cerebrum**—Stimulant action of atropine antagonizes depressant effect of morphine. Alertness and mental lucidity persist but somewhat obtunded. Amnesia not common unless large doses are used.

**Respiratory Center**—Stimulating effect of atropine antagonizes depressant action of morphine

**Vasomotor Center**—Barely affected unless large doses are given.

**Heart Center**—May be stimulated initially yielding bradycardia. Tachycardia may follow due to peripheral action of atropine on vagus.

**Metabolic Rate**—Reduced, but less than when morphine is used alone due to stimulant action of atropine

**Respiration**—Moderate decrease in minute volume exchange. No effect on pulmonary time

**Skin**—Dryness, flushing, absence of sweating frequently occurs.

**Thalamus**—Pain perception decreased due to analgesic action of morphine

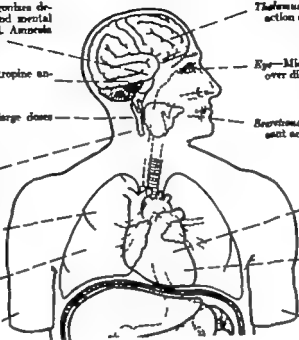
**Eye**—Miosis. Morphine effect usually predominates over dilating effect of atropine

**Sarotrans**—Inhibited due to parasympathetic depressant action of atropine.

**Heart**—Some elevation in pulse rate frequently occurs. Tachycardia not common (vagal depression)

**Blood Pressure**—Usually reduced if elevated from excitement no change otherwise

**Body Temperature**—May be elevated due to effect of atropine centrally and on skin.



## MORPHINE-SCOPOLAMINE

Morphine and scopolamine in the ratio of 25 parts to 1 respectively administered intravenously 10 minutes prior to anesthesia or subcutaneously one and one half hours prior to anesthesia produces the following effects

**Cerebrum**—Depression causing excellent sedative effect. Apprehension allayed. Amnesia frequent. Euphoria and feeling of well being common. Sedative effects of scopolamine are additive to those of morphine

**Heart Center**—May be stimulated initially. Usually no remarkable effect.

**Vasomotor Center**—Not affected ordinarily. Over-excitation may cause hypertension.

**Respiratory Center**—Depression caused by morphine is antagonized by scopolamine. Usually remains in pre-anesthetic state of excitation.

**Respiration**—Slight decrease in minute volume exchange. No notable effect on oxygenation.

**Metabolic Rate**—Decrease in oxygen consumption 10 to 15%.

**Skin**—Cool. No flushing or dryness.

**Thalamus**—Pain perception reduced due to analgesic action of morphine.

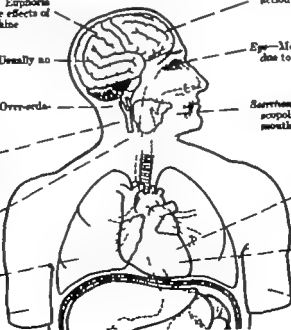
**Eye**—Morphine action predominates. Miosis common due to parasympathetic stimulation by morphine

**Sarotrans**—Parasympathetic depressant action from scopolamine inhibits secretions and causes dryness of mouth.

**Heart**—No change in rate. Slowing occurs if tachycardia from excitement exist prior to anesthesia.

**Blood Pressure**—Reduced if elevation exists from excitement prior to anesthesia; otherwise no effect.

**Body Temperature**—No change. May be reduced.



# SECTION XIV SOME CLINICAL CONSIDERATIONS

## PRE-ANESTHETIC MEDICATION

Reasons for administering premedication and drugs used are as follows:

- (1) For psychic sedation—barbiturates, opium alkaloids, veratrin.
- (2) To obtain an additive or synergistic effect—(opium alkaloids, demerol, procaine methedon) between drugs and contemplated anesthetic agents.
- (3) To reduce reflex irritability and metabolic rate—opium alkaloids, veratrin.
- (4) To suppress secretions—atropine, scopolamine.
- (5) Prophylactically to overcome undesirable anticipated side effects caused by the anesthetic agent.

**Nervous System**—Psychic sedation causes depression of cortex and calms patient. Analgesic drugs suppress pain and decrease reflex irritability. Second stage shortened when patients are sedated. Drugs depressing cortex, medulla and other centers antagonize stimulating action of local anesthetics.

**Respiratory System**—Depressant drugs decrease O<sub>2</sub> consumption. Induction and maintenance of anesthesia. Its agents requiring high partial pressure are facilitated by this response.

**Bronchi**—Vagal reflexes from stimulation locally or manipulation of lumen inhibited.

**Metabolism**—Reduced by central nervous system depressant. Dosage of premedicating drug must be adjusted in following factors:

- (a) *d<sub>pm</sub>*—Metabolic rate decreases with age. Less premedicating agent necessary. Metabolic rate highest in infancy.
- (b) *%a*—Variation in metabolic rate between sexes of minor significance. Rate increased in puberty.
- (c) *F<sub>ees</sub>*—Increases metabolic rate markedly (7 calories per degree F). Dosage may be increased.
- (d) *F<sub>am</sub>*—Increases metabolic rate. More premedicating agent required.

**Dosage of Metabolism**—Thyrotoxicosis necessitates increased dosage of premedicating agent. Hypothyroidism requires decreased dosage. Cachexia reduces metabolic rate profoundly.

**Nervous Secretions**—Parasympathetic depressants (atropine, scopolamine) inhibit salivary and mucous secretions.

**Larynx**—Spasms of central origin inhibited by parasympathetic depressant (atropine).

**Circulatory System**—Blood pressure and pulse approach normal due to release of psychic influence.

**Prophylaxis**—Parasympathetic drugs (atropine) given to counteract vagal stimulation. Drugs exerting parasympathetic action gives in anticipation of circulatory failure (epidural in spinal anesthesia).

**Muscular Reflexes**—Traction on visceral structures inhibits circulatory and respiratory disturbances. Inhibited by atropine.

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**Regional Anesthesia**—For adult of average size morphine gr  $\frac{1}{2}$  and scopolamine gr 1/100 intramuscularly supplemented by a therapeutic dose of a short acting barbiturate such as pentobarbital or veratrin. For spinal anesthesia the barbiturate is omitted.

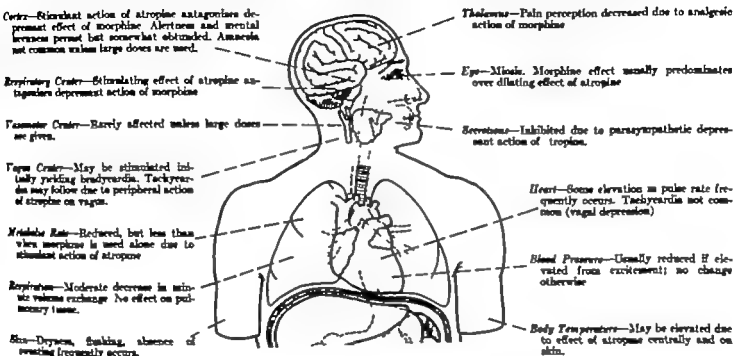
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**For Psychically Disturbed or Extremely Apprehensive Patients**—Basal narcosis with veratrin, rectal or intravenous pentobarbital or oral or paralytic may be used.

**For Subjects Intolerant to Morphine**—Dilaudid, demerol, methedon or ponton may be used.

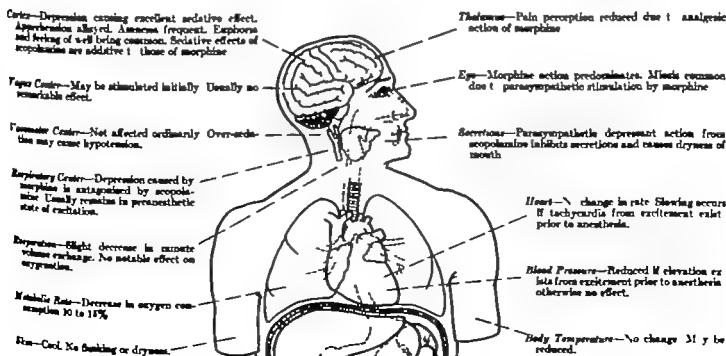
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## DEPTHS OF GENERAL INHALATION ANESTHESIA FOR SURGERY

Third stage of anesthesia required for surgery Divided into four planes or strata (after Goedel) as follows:

**1st**—Lid reflex or tone disappears, eyeballs occlude; pupils return to pre-anesthetic size; inspiration equals expiration. (No remarkable circulatory changes.)

**2nd**—Eyeballs fixed; progressive intercostal paralysis; thoracic inspirations delayed; expiration prolonged. (Circulation fails.)

**3rd**—Eyeballs fixed, pupils increase in size; rhythmic respiration quickened, expiration prolonged. (No remarkable circulatory changes.)

**4th**—Pupils dilate; diaphragmatic respiration; quick, jerky inspiration; prolonged expiration. (Circulation fails.)

Signs may vary with agent and subject pass in reverse on transition from deep to light anesthesia.

**Craniotherapy**—1st plane: no pain in handling brain. No relaxation required. Intratracheal tube necessary for airway.

**Masticatory**—1st plane sufficient; no relaxation required. Intratracheal tube desirable.

**Myriapathy**—1st plane: should not be attempted without anesthesia.

**Laryngeal**—Upper end: some muscle relaxation required.

**Thoracic**—1st and 2nd plane: no muscle relaxation needed. Intratracheal catheter required.

**Cholegastrotherapy**—Lower end: plane, some (tunes 3rd); adhesion of vocal cords frequent, best relieved by intratracheal tube.

**Asphyxiatory**—2nd and 3rd plane: minor traction reflexes may be active. Position often necessitates use of intratracheal tube.

**Ventral Perineurotherapy**—Lower end: plane, sometimes upper 3rd. Relaxation necessary.

**Apophyseal**—2nd and 3rd plane.

**Femoral and Ischiopubic Perineurotherapy**—2nd plane; some muscle relaxation needed.

**Urethral and Ovariotherapy**—Perineal, vaginal and cervical, 1st plane: intra-abdominal, 2nd and 3rd planes.

**Proctal**—For sphincter relaxation, 3rd plane.

**Fractures**—For bones attached to small muscles, 1st plane; to large muscles, 2nd plane.

**Incision and Drainage**—1st plane for superficial abscesses.

**Ophthalmic**—1st plane: small muscles relax easily. In 2nd plane, 2nd plane if intratracheal tube is used.

**Vocal and Flaccid**—1st plane sufficient, no relaxation required. 2nd plane if intratracheal tube is used.

**Pharyngeal Surgery**—Tolerated in 1st plane intratracheal in 2nd plane.

**Tonsillectomy**—2nd plane: relaxation of muscles necessary. Intratracheal catheter desirable.

**Thyroidectomy**—1st plane: no relaxation of muscles necessary. Intratracheal catheter desirable.

**Mediastinal Explorations**—2nd plane. Intratracheal tube required.

**Cardiac Surgery**—2nd plane. Intratracheal tube required.

**Diaphragmatic Surgery**—3rd plane. Intratracheal tube required.

**Rectotomy**—1st plane. Muscle relaxation not necessary.

**Splanchnic**—Lower end or 3rd plane: muscle relaxation required.

**Gastro**—Lower end or 3rd plane: muscle relaxation required.

**Intestinal**—During enterostomy, upper end or lower 1st plane, with deepening of anesthesia on closure; 2nd or 3rd plane for resections, little or no pain in handling viscera.

**Obstetrical**—Normal delivery: analgesia or 1st plane; forceps delivery: 1st to 2nd plane; breech delivery: 2nd plane; version, 3rd plane; Bland's ring, 4th plane; Caesarean section, upper end (abdominal muscles stretched, little relaxation needed).

**Amputation**—1st plane.

**Tenotomy**—1st plane for small muscles; 2nd plane with large muscles, nerves, large trunks, 2nd plane.

Requirements for individual cases vary with subject, anatomical variations, and requirements of the surgeon.





## DEPTHS OF GENERAL INHALATION ANESTHESIA FOR SURGERY

Third stage of anesthesia required for surgery Divided into four planes or strata (after Guedel) as follows

1st—Lid reflex or tear disappears, eyeballs everted; pupils return to pre-anesthetic size; inspiration equals expiration. (No remarkable circulatory changes.)

2nd—Eyeballs fixed; progressive intercostal paralysis; thoracic inspirations delayed; expiration prolonged. (Circulation falls.)

3rd—Eyeballs fixed; pupils increase in size; rhythmical respiration; inspirations quickened; expiration prolonged. (No remarkable circulatory changes.)

4th—Pupils dilate; diaphragmatic respirations; quick, jerky inspirations; prolonged expiration. (Circulation fails.)

Signs may vary with agent and subject pass in reverse on transition from deep to light anesthesia.

**Cranioctomy**—1st phase: no pain in handling brain. No relaxation required. Intratracheal tube necessary for airway.

**Mastoidectomy**—1st phase sufficient; no relaxation required. Intratracheal tube desirable.

**Meningocele**—1st phase: should not be attempted without anesthesia.

**Laminectomy**—Upper end: some muscle relaxation required.

**Thoracic**—1st and 2nd phase: no muscle relaxation needed. Intratracheal catheter required.

**Cholecystectomy**—Lower end: 2nd phase, sometimes 3rd; adhesion of vocal cords frequent, best relieved by intratracheal tube.

**Vagotomy**—2nd and 3rd phase: minor traction reflexes may be active. Position often necessitates use of intratracheal tube.

**Frontal Hemispherectomy**—Lower end: 2nd phase sometimes upper 3rd. Relaxation necessary.

**Appendectomy**—2nd and 3rd phase.

**Frontal and Infratemporal Hemispherectomy**—2nd phase: some muscle relaxation needed.

**Urethral and Ovariohysterectomy**—Perineal, vaginal and cervical, 1st phase: intra-abdominal, 2nd and 3rd phases.

**Rectal**—For sphincter relaxation, 3rd phase.

**Fractures**—For lower: (small muscles, 1st phase; large muscles, 2nd phase).

**Incisions and Drainage**—1st phase for superficial abscesses.

**Ophthalmology**—1st phase: small muscles relax easily in light second phase, 2nd phase if intratracheal tube is used.

**Nasal and Plastric**—1st phase sufficient, no relaxation required. 2nd phase if intratracheal tube is used.

**Pharyngeal Surgery**—Tolerated in 1st phase; intratracheal in 2nd phase.

**Tonsillectomy**—2nd phase: relaxation of muscles necessary. Intratracheal catheter desirable.

**Thyroidectomy**—1st phase: no relaxation of muscles necessary. Intratracheal catheter desirable.

**Mechanical Explorations**—2nd phase: intratracheal tube required.

**Cardiac Surgery**—2nd phase: intratracheal tube required.

**Diaphragmatic Surgery**—3rd phase: intratracheal tube required.

**Mastectomy**—1st phase: muscle relaxation not necessary.

**Splenectomy**—Lower end or 3rd phase; muscle relaxation required.

**Omentum**—Lower end or 3rd phase; muscle relaxation required.

**Intestinal**—During enterostomy, upper end or lower 1st phase with deepening of anesthesia on closure; 2nd or 3rd phase for re-sections, little or no pain in handling viscera.

**Obstetrical**—Normal delivery: analgesia or 1st phase (forceps delivery: 1st to 2nd phase); breech delivery: 2nd phase; version, 3rd phase; Bandl's ring, 4th phase; Cesarean section, upper end (abdominal muscles stretched, little relaxation needed).

**Amputations**—1st phase.

**Tracheotomy**—1st phase for small muscles; 2nd phase with large muscles. Nerves, 1st phase; large trunks, 2nd phase.

Requirements for individual cases vary with subject, anatomical variations, and requirements of the surgeon.

## DISTURBANCES OF RESPIRATION

 $O_2$ - $CO_2$  Transport

(a)—By volume composition is—

$O_2$	20.9%
N	78.0%
$H_2O$	1.0%
$CO_2$	0.04%
rare gases (not essential to life)	0.01%
dust, moisture	q.s.

Area of Alveoli—100 square meters.

Resting State of Lungs—At end of expiration.

 $O_2$  Tension— $O_2$  in alveoli, 10.3%—103 mm. Hg.

$CO_2$  Tension— $CO_2$  in alveoli, 3.1 to 3.5%, 40 mm. Hg. average. Concentration varies 0.1 to 0.6% between inspiration and expiration; 66% tidal air mixes with alveolar air causing gradual variation of gas tensions along tract and preventing abrupt changes in concentration.

Airway—Distance from lips to larynx—16.1 cm.; length of larynx—4 to 6 cm.; larynx to trachea—16 to 18 cm.; diameter of trachea—2.5 cm.; diameter shorter in female than male and in children and young adults.

Blood  $CO_2$ —Total % arterial content  $CO_2$ —48 vols. % venous—47 vols. % in three forms—dissolved—3 vols. % to 1% as  $H_2CO_3$ , rest as free  $CO_2$ ; carbamino—4 vols. %; and bicarbonate makes up remainder.

Chloride Shift— $CO_2$  diffuses into cell, changed to  $H_2CO_3$ , in less than one second with aid of carbonic anhydrase; Cl ion from plasma diffuses in and bicarbonate diffuses out. K ion in cell from breakdown of oxyhemoglobin then becomes available to combine with Cl ion.

Bicarbonate passes to lung with a ion of plasma.  $O_2$  forms oxyhemoglobin in cell which is more acid and which combines with a ion. Cl ion diffuses out; bicarbonate ion diffuses in; same exchange reverses action, liberating  $CO_2$ , which diffuses into plasma and alveoli.

Inspired Air  $O_2$  Tension—158 mm. Hg.Expired Air  $O_2$  Tension—116 mm. Hg.

Resting Minute Volume Exchange—Eight to 10 liters per minute. May increase to 80 liters with extreme exertion.

Tidal Air—An ordinary inspiration or expiration at rest equals 500 cc.

Capacity of Lungs—Power to five liters total.

Dead Space—(Anatomical) Air space in trachea, pharynx and bronchi amounts to 180 cc. 33% of tidal air remains in dead space. 66% mixes with functional residual air. Physiological, virtual or effective dead space is total space in lungs which just prior to expiration contains perfectly fresh air.

Tidal Capacity—From onset of maximum inspiration to end of maximum expiration averages 3500 cc.

Reserve Air—From end of ordinary expiration to end of maximum expiration averages 1500 cc.

Complemental Air—From end of maximum inspiration to end of quiet expiration averages 800 cc.

Residual Air—Air remaining in lung after maximum expiration averages 1000 cc.

Blood Volume—80 cc. per kilo.; plasma 30 cc. per kilo.  $O_2$  carried by plasma—0.31 vols. %;  $O_2$  carried by hemoglobin—18 vols. %; 1 gm. hemoglobin carries 1.34 cc.  $O_2$  normal hemoglobin equals 12 gm. per 100 cc.,  $O_2$  tension in blood—100 mm. Hg. arterial blood, 93% saturated, venous blood saturation varies, averages 83%, A-V difference, 4 vols. %; pure  $O_2$  quadruples plasma  $O_2$ .

Fetal Blood—Arterial blood carried by umbilical vein  $O_2$  capacity averages 22 vols. %; 60% saturated; venous blood carried by umbilical arteries contains 4 vols. % arterial blood total  $CO_2$  content, 44 vols. %,  $CO_2$  tension higher than maternal blood allowing outward diffusion.  $O_2$  tension lower than maternal, allowing inward diffusion.

## ANOXIA

In acute anoxia three stages may be discerned (1) A *pre-crisis stage*—occurs when approximately 12 volumes per cent oxygen is present in arterial blood (2) a *circulatory crisis stage*—occurs when approximately 8 volumes per cent are present in arterial blood (3) a *terminal stage*—occurs when approximately 4 volumes per cent are present in arterial blood

**Brain**—Physiologically newer cells most sensitive of all tissues due to high rate of oxygen consumption. Progressive depression of central nervous system from above downwards occurs as degree of anoxia increases. Physiologically older portions of brain more resistant than newer.

**Medulla**—Depressed. More resistant than the cortex.

**Cerebrum**—Heavily stimulated by mild anoxia (pre-crisis stage). Depressed in terminal stage. Cortex depressed. Respiratory center before vasomotor. Vagus center last.

**Respiratory Movements**—Pre-crisis stage—Increase in both depth and rate (also aortic stimulation). Crisis stage—regular breathing ceases. Apneustic groups appear. Terminal stage—respiration ceases.

**Mentation**—Affected. Usually depressed.

**Liver**—Impairment of function occurs, depending upon duration and severity of anoxia and state of organ.

**Adrenal**—Epinephrine content of gland depleted by mild anoxia. Signs of sympathetic stimulation appear.

## BLOOD

**Total Volume**—Reduced. Capillary permeability increased.

**Red Blood Cells**—Increased. Result of hemoconcentration.

**Carbon Dioxide Content**—Reduced at first due to hyperventilation. May increase later.

**Carbon Dioxide Combining Power**—Reduced due to liberation of fixed acids.

**Lactic Acid**—Increased, due to oxygen debt.

**Glucose**—Increased due to glycogenolysis.

**Clotting**—Blood remains in fluid state past normal.

**Cortex**—Highly sensitive to oxygen deprivation. Motor cells irritated causing various neuromuscular phenomena.

**Eye**—Nystagmus at first. Eyeball fixed. Pupils dilate due to depression of centers. Corneal reflexes and light reflexes lost in crisis stage.

**Trachea**—Spasm of vocal cords in crisis stage. Relaxed in terminal stage.

**Salivary Glands**—Yield scant amount of thick mucus.

**Blood Pressure**—Pre-crisis stage: Systolic increases, diastolic unaltered or lowered. Pulse pressure increased. Crisis stage: Systolic falls. Terminal—rapid fall to zero of both systolic and diastolic.

**Heart**—Pre-crisis stage: Acceleration due to disinhibition of vagal tone. Heart dilates. Crisis stage: Bradycardia and finally occurs, mediated by cardio-inhibitory nerves. Gradually as anoxia increases pulse rate increases (cardio-inhibitory center is depressed). Terminal stage: Direct depression of myocardium occurs. Shocking followed by asystole.

**Venous Pressure**—Rise in venous pressure in pre-crisis and in crisis stage.

**Spleen**—Constricted due to sympathetic stimulation. Red cells pass into systemic circulation.

**Stomach**—Hunger contractions decreased. Secretions not inhibited.

**Intestine**—Motility depressed.

**Muscles**—Twitchings followed by convulsions (clonus, opisthotonus, tetanic spasms, extreme spasm) and generalized convulsions are manifestations of cortical irritations. Central nervous system depressants may soften or completely mask them.

**Skin**—Cyanosis appears when concentration of reduced hemoglobin exceeds 4 grams %. Intensity varies with:  
(1) caliber of cutaneous vessels,  
(2) thickness of skin,  
(3) amount of pigment in skin,  
(4) acuity and color perception of observer.  
Skin temperature reduced. Vessels constricted.

Symptoms and effects of anoxia vary from individual to individual and with degree and duration. Anesthesia modifies signs and symptoms of anoxia. Anoxia is O<sub>2</sub> lack without impediment to CO<sub>2</sub> elimination. Asphyxia denotes impediment to CO<sub>2</sub> and O<sub>2</sub> exchange.

## TYPES OF ANOXIA

1. *Anoxic*—Amount of oxygen passing through the alveolar membrane insufficient to saturate completely blood in pulmonary vascular bed. Content and tension reduced.
2. *Stagnant*—Amount of oxygen delivered to tissues insufficient due to poor circulation. Content and tension normal.
3. *Anemic*—Amount of oxygen carrying pigment reduced. Content decreased, tension normal.
4. *Histotoxic*—Ability of cells to utilize oxygen reduced. Blood oxygen content normal or increased.

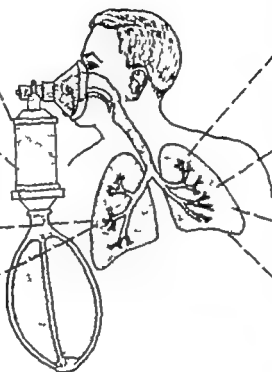
## CAUSES OF ANOXIA OR ASPHYXIA

1. Insufficient oxygen in inhaled mixture

2. Reduced tidal exchange (anoxic asxia) May be caused by depressed respiratory center or carotid body. Intercostal paralysis, convulsions, compression of thorax, pneumothorax, hydrothorax, pyothorax, Tyrodeberg and other poisons which inhibit respiratory motion.

3. Obstruction. Secretions, reduced tongue or muscles, spasm of vocal cords from various causes such as excessive high concentration of the drug, blood, vomitus, caustic dust, CO<sub>2</sub>, foreign body tracheal collapse or neoplasms encroaching upon trachea or bronchi and bronchioles from allergic states or effect of the drug.

4. Decreased vital capacity (anoxic asxia) Pulmonary decompression due to emphysema, neoplasms, fibrosis or sequestrative disease.



5. Interference with diffusion (anoxic asxia) Edema of alveolar membrane, excessive secretions, emphysema or inflammatory lesions.

6. Failure of transport system (stagnant anoxic) Myocardial insufficiency, prolonged circulation time due to shock or hemorrhage, obstruction to blood flow due to emboli from air, fat or clots.

7. Decrease in oxygen carrying power (anemic anoxic) Anemia, reduced blood volume, alterations in hemoglobin such as carbon monoxide hemoglobin.

8. Disturbances of tissue respiration (histotoxic anoxic)—cyanides and arsenic may inhibit respiratory enzymes.

## SYMPTOMS OF CEREBRAL DAMAGE

Ordinarily occur after a bout of acute anoxia which was characterized by both respiratory and circulatory failure. Distortion of the cerebral vessels and stasis occurs.

*Immediate Signs*—Slow bounding pulse, irregular gasping respiration, followed by apnea. After resuscitation, coma, followed by twitching of small muscles, convulsions and muscle rigidity occur. Hyperthermia within six to 64 hours is usual terminal event (104° to 110°F. not uncommon).

*Delayed Signs*—Gradual emergence from above poore. Superficial decubiti, with gradual recovery. Parkinsonism, blindness, or psychosis often occur. May be transient, lasting weeks or months, or permanent.

*Pathological Effects of Asphyxia*—Cerebral damage follows respiratory and circulatory failure or protracted bouts of asphyxia. Petechial hemorrhages may be found on serous surfaces of various organs due to changes in capillary permeability in acute asphyxia. No changes elsewhere.

When death is delayed changes are found in brain. Occur mostly in cortex, cerebellum and basal ganglia, but may appear anywhere in the C.N.S.

## PATHOLOGICAL CHANGES IN BRAIN

## CORTEX

*Earliest Changes*—Occur several hours after respiratory and circulatory failure. Widened perivascular and pericellular spaces most common finding.



*Late Changes*—Death of cells followed by vacuolization and confluence of areas of necrosis.

*Healed*—Necrotic areas replaced by scar tissue. Nervous elements do not regenerate. Similar changes noted if death is delayed for weeks or months.

*Nerve Cells*—Pyramidal and Purkinje's cells undergo acute degeneration. Chief findings are swelling of cytoplasm, nuclear degeneration and disappearance of Nissl substance followed by necrosis.

*Interneural Cells*—Changes occur in microglia. Astrocytes proliferate and oligodendroglia atrophy.

*Meninges*—Adhesions between pia, arachnoid, and dura follow inflammatory changes resulting from death of tissue.

## EFFECTS OF ANOXIA ON CIRCULATION AND RESPIRATION DURING INHALATION ANESTHESIA AND HYPNOSIS WITH NON VOLATILE DRUGS

Agent	Crisis Stage					Terminal Stage			
	Blood Pressure	Heart Rate	Vagal Tone	Respiration Apneustic gasping	Chemoreceptor Activity	Blood Pressure	Heart Rate	Vagal Tone	Respiration
Nitrogen	Elevated	Slowed	Increased	Present	Active	Falls	Slowed	Decreased	Ceases
Nitrous oxide	Elevated	Slowed (vagal effect)	Increased	Present	Active	Falls	Slowed, followed by asystole	Depressed	Ceases
Nitrous oxide Atropine	Elevated	Increased	Depressed by the premedication	Apneustic gasping does not appear	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Nitrous oxide Morphine	Elevated	Increased	Depressed by premedication	Present mildly masked	Mildly depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Nitrous oxide Pentobarbital	Elevated	Increased	Depressed by barbiturate	Absent	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Nitrous oxide Amytal	Elevated	Increased	Depressed by barbiturate	Absent	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Ether III 1 & 4	Elevated	Slowed (vagal)	Increased	Present	Mildly depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Ether III 3 & 4	Elevated	Increased	Depressed by drug	Absent	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Pentothal	Elevated	Increased	Depressed by drug	Absent	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Cyclopropane	Elevated	Slowed (vagal)	Increased	Present	Active	Falls	Slowed, followed by asystole	Depressed	Ceases
Chloroform	Elevated	Slowed (vagal)	Increased	Present	Active	Falls	Slowed, followed by asystole	Depressed	Ceases
Diethyl	Elevated	Slowed	Increased	Present	Active	Falls	Slowed, followed by asystole	Depressed	Ceases

"Slow bounding pulse" and apneustic gasping are attended by certain agents and premedication, thereby increasing possibility of passing without warning from pre-crisis to crisis stage.

## ALTERATIONS IN PULMONARY PHYSIOLOGY DURING GENERAL ANESTHESIA

**Anatomic Dead Space**—Increased by agents which decrease bronchial tone, decreased by agents which increase bronchial tone.

**Physiologic Dead Space**—Increased by increased tidal volume or mechanical ventilation.

**Diffusion Respiration**—Interchange of gases between blood, alveoli, and upper respiratory tract which occurs in the absence of respiratory movements. Induced by having high  $O_2$  partial pressure in upper respiratory tract. Alveolar  $O_2$  combines with hemoglobin, decreases alveolar pressure, and causes inward diffusion of  $O_2$  (called hemoglobin pump). Ours and diffusion of  $CO_2$  occurs but more slowly. Results in  $CO_2$  retention and severe metabolic acidosis.

**Diffusion Anoxia**—Anoxia resulting from out and diffusion into the alveoli of highly soluble gases administered at high partial pressures. Occurs when  $N_2O$  anesthesia is interrupted and air breathing is commenced. One volume of poorly soluble  $N_2$  replaces 36 volumes of  $N_2O$  from blood. Lung gives up gas volume. Outward rushing of excess gas dilutes  $O_2$  in lung. Causes anoxia.

**Breathy**: Terminate anesthesia inhaling 100%  $O_2$ .

**Mucous Failure**—Decreased due to central depression and decreased metabolic needs.

**Resistance**—Impedance to passage of respiratory gases. Varies with bronchial diameter, viscosity, density, and degree of turbulence of gases, and mechanical factors in lumen. Increased resistance necessitates increase in respiratory effort.

**Inspiratory Resistance**—Necessitates increased respiratory effort to maintain normal alveolar volume exchange and blood gas tensions. Causes increases in negative pressure in alveoli and pleural space. May lead to pulmonary edema.

**Expiratory Resistance**—Less fatiguing than inspiratory. Agents which increase bronchial tone decrease anatomic dead space.

**Controlled Respiration**—Artificially maintaining pulmonary ventilation by deliberately reducing apnea. Apnea produced by (1) combination of (a) reducing  $CO_2$  tension (hyperventilation), (b) depression of respiratory center (a) drugs (cyclopropane and a narcotic), (c) stimulation of stretch reflexes, or (d) neuromuscular blockade (curare). May increase physiologic dead space during unexpectation.

**Pleural Pressure**—Prolonged positive pressure causes decreased venous return and decreased cardiac output. Intermittent positive pressure low diastolic pressure if deflation time causes induction time and collapse pressure returns to normal.

**Yippee Pressure**—May result in collapse of respiratory bronchioles in pathological states: emphysemas.

**Effect of Body Position**—Supine prone or lateral causes decrease in functional residual air volume.

**Latent**—upper lung under-perfused and over-ventilated. Dependent portions under-ventilated, over-perfused. Dead space increased,  $CO_2$  retained.

**Upper Respiratory Tract Reflexes**—Mediated via the vagus nerves. Stimulation by pungent agents (ether, chloroform) reflexly inhibits inspiration. May cause apnea and glottic spasm. Less pronounced stimulation by gases.

**Lower Pulmonary Tract Reflexes**—Receptors (stretch) activated by distention and by collapse (deflation). Served by vagus. Vapors (ether, chloroform, fluothane, trichloroethylene, etc.) sensitize both stretch and deflation receptors. Augment ventilation. Sensitization by gases sufficient to augment ventilation.

**Extra-Pulmonary Sensory Receptors**—Sensory receptors (in muscles, joints, etc.) communicating with respiratory system stimulated by blood borne anesthetics and augment respiration (ether).

**Lung Volume**—V men. Probably decreased during general anesthesia. Functional residual air capacity less in supine than erect or lateral position. Stretch receptors reflexly alter resting lung volume during positional changes.

**Compliance**—Stretch-ability of lung. Defined as volume change of lung and thorax per unit of pressure change at zero air flow. Expressed in liters per cm.  $H_2O$  pressure between trachea and pleura. Compliance varies with (1) elasticity of lung, (2) lung blood volume, (3) tone of thoracic muscles cage, (4) total lung tissue mass, (5) tendency of alveoli to collapse, (6) bronchial tone. Increase in compliance necessitates increase in respiratory effort.

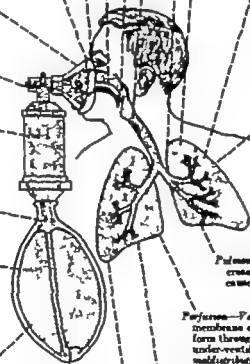
Alterations during anesthesia variable. Generally decreased. Factors favoring decrease are: (1) Bronchial obstruction (constriction, secretions, mucosal edema), (2) vascular stasis due to effects of agents, (3) changes in pleural muscle tone, (4) influence of vagal reflexes (stretch-deflation), (5) mechanical factors causing uneven ventilation of lung.

**Pulmonary Circulation**—Pulmonary vascular resistance increases during anesthesia (ether). Lung inflation also causes increase.

**Perfusion**—Ventilation Ratio—Gas transfer across pulmonary membrane optimal when ratio of blood flow to gas flow is uniform throughout all areas of lung. Under-perfusion, over-perfusion, under-ventilation or over-ventilation in any area results in maldistribution. Maldistribution alters  $O_2$  and anesthetic gas uptake and  $CO_2$  elimination. Over-perfused (under-ventilated) areas result in low anesthetic and  $O_2$  uptake. Equivalent to creation of A-V shunt. Under-perfused (over-ventilated) equivalent to increase in alveolar dead space. Hypoventilation causes increased alveolar  $CO_2$  and changes in gradient from blood to alveolar air due to collapse of some alveoli.

**Open Pneumothorax**—Results in maldistribution. Over-perfused and under-ventilated in collapsed lung. Blood gas tensions disturbed. Respiratory alkalosis, anoxia due to creation of shunts and collapsing of alveoli.

**Closed Pneumothorax**—May cause greater distress by collapse of lung due to tension.



## RESPIRATORY ACIDOSIS DURING GENERAL ANESTHESIA

**DEFINITION**—Elevation in  $\text{CO}_2$  tension, total acids of blood and decrease in blood pH due to faulty elimination of  $\text{CO}_2$ .

**Causation During Anesthesia**—Hypoventilation from depressed respiratory center; impaired ventilation due to maldistribution of gases, improper pulmonary perfusion, obstruction and other mechanical factors. Occurs with all anesthetics. Least with ether.

**Central Nervous System**—Carbon dioxide excess depresses all areas. An additive effect results with anesthetics. Arterial blood ether concentration for given E.E.G. level less due to additive effects of  $\text{CO}_2$ . May produce convulsions if pyrexia and metabolic acidosis complicate anesthesia.

**Vagus**—Respiratory acidosis enhances the effect of vagal stimulation on the heart.

**Carotid Body**—Remains active. Stimulated only by very high  $\text{CO}_2$  tensions.

**Respiratory Effects**—Variable. Hypoventilation usually present. Hyperpnea uncommon due to depression by agent. Hypoventilation enhanced by non-volatile hypnotics and paralytics. Respiration may be gasping in severe states.

**Arterial  $\text{CO}_2$  Tension**—Elevated. May rise from 47 to 160 mm. Hg in severe states. Average increase 15–80 mm. Hg above normal.

**Diaphragm**—Spasmodic jerking of diaphragm (hiccough).

**Metabolism**—Some suppression of liver functions. Ability of liver to metabolize thiopental decreased by hypercarbia.

**$\text{CO}_2$  Output**—Total output decreased due to increased metabolism. Concentration of expired gas increases. V rises with degree of ventilation (1–2%—3–4 normal).

**Kidney**—Increased excretion of acid. Loss of base results. Prolonged respiratory acidosis may merge but metabolic acidosis. Ketone bodies not increased.

**Alveolar Temperature**—Elevated due to peripheral vasodilatation. Cyanosis. Local in face of adequate  $\text{O}_2$  intake.

**Intracranial Pressure**—Increased. Cerebral vessels dilated. Cerebral blood flow increased.

**Pupils**—No changes in size. Activity of ocular reflexes diminished due to effects of carbon dioxide narcosis on anesthesia.

**Heart**—In mild degrees of acidosis no change. In severe cases marked bradycardia and irregularities in rhythm occur. Increases in amplitude of T waves. Abrupt decrease in  $\text{CO}_2$  may cause ventricular asystole or ventricular fibrillation. Gradual decrease may not. Contractile force of the heart decreased in severe acidotic states.

**Blood Pressure**—Peripheral resistance increases as  $\text{CO}_2$  tension becomes elevated. Pressure elevated. Abrupt lowering of  $\text{CO}_2$  tension causes sudden reduction in blood pressure below baseline—hypotension results. Diastolic decreased abruptly. Decrease varies with degree of  $\text{CO}_2$  accumulation. Hypotension results from sudden withdrawal of vasoconstrictor reflex and persistence of local vasodilator effect of hypercarbia. May follow anesthesia with any agent during which  $\text{CO}_2$  retention occurs.

**Central Venous Pressure**—Increased. Reduction if hypotensive state develops.

**Arterioles**—Dilated. Effect persists after withdrawal of excess  $\text{CO}_2$ . Contributes to hypotension after removal of central vasoconstrictor drive.

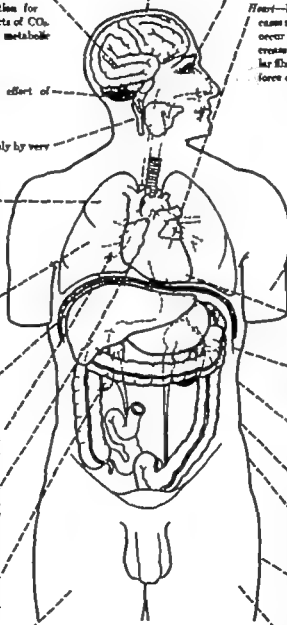
**Capillaries**—Dilated by  $\text{CO}_2$  excess. Contributes to increased swelling.

**Clotting Time**—Shortened.

**Electrolytes**—Arterial blood pH decreased below 7. Plasma potassium rises. May reach 7.0 or more M.E.Q. Goes lost into urine.

**Effect of Position**—Lateral and other restrictive positions favor retention of  $\text{CO}_2$  by causing maldistribution of perfused blood and alveolar gases.

**Body Temperature**—Decreased body temperature favors  $\text{CO}_2$  retention due to increased solubility plasma (hypothermia).



## THE ELECTROENCEPHALOGRAM IN ANESTHESIA

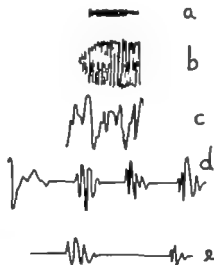
**DEFINITION**—The brain produces electrical activity measurable in terms of potential. Electroencephalogram is a graphic record of the sum of the voltages developed by individual neurons in a particular area of the cerebral cortex. Usually the activity of an area of the cortex is measured. Origin of electrical activity of cortex not fully understood. Presumably rhythms represent fluctuating potentials produced by dendrites. Minute electrical impulses passing through intact skull and scalp are gathered by electrodes and conducted through amplifiers. Amplified current operates a system of levers which records variations in intensity of current graphically with ink-writers. Current rises from zero to maximum, reverts back to zero many times per sec., resulting in a tracing consisting of waves called cycles. Height (amplitude) of wave is governed by voltage developed. Number of waves (frequency cycles) varies with different stages of activity. Normally three wave patterns are noted. (1) Alpha (awake with eyes closed) about 10 cycles per sec., 50 millivolts—obtained from occipital areas. (2) Beta—20 to 30 cycles per sec. 5–10 millivolts. (3) Delta—1 to 5 cycles per sec., voltage increased 80 to 900 microvolts—occurs in sleep and in pathologic states in awake persons.

**HISTORY**—Electrical activity first noticed by Caton (1875). Von Harrow first studied alterations caused by chloroform (1890). Hans Berger (Jena, 1929) founded science of electroencephalography. Gibbs and Lennox (1937) suggested electroencephalogram might be applicable to anesthesia. Rubin and Freeman (1940) studied changes during cyclopropane anesthesia. Brainer and Finesinger (1945) studied effects of barbiturates on cortical potentials. Beecher and McDonough studied cortical potentials with seventeen anesthetic agents (1939). Bickford and Faulkner (1950) classified electroencephalographic changes produced by ether and other anesthetics.

### USES IN ANESTHESIA

Cortical potentials altered by central nervous system depression. Suppression is proportional to the quantity in the brain. Changes produced are (1) reproducible for given drug in given patient, (2) vary little from person to person for given drug, (3) the discharge is serial—disappears and reappears in same manner as concentration is varied, (4) response is rapid.

Clinical signs of reflex activity (Gurdell) lag behind return of cortical activity to normal. (5) The brain discharges as a unit. Local differences disappear and synchronization of activity of the cortex appears. (6) Rhythms simplified. (7) The stages of depression are correlated with blood concentration (volatile drugs).



### BASIC CHANGES IN PATTERN

Basic changes in pattern are common to many drugs. These are:

- Increase in frequency in 20–30 cycles per sec. N voltage change (as consciousness is lost).
- Small waves rapid, replaced by larger (5–300 microvolts) at slower rhythm 1–5 cycles per sec. as consciousness is lost.
- Fast low voltage waves superimposed on background of high voltage, low frequency. Also known as mixed pattern.
- Voltage decreases, frequency decreases with periods of inactivity interspersed between periods of activity. Inactivity separated by activity called burst suppression. Interval of inactivity becomes longer and number of waves decreases as anesthesia deepens.
- Loss of activity flat tracing or low voltage very slow rhythm occurs in over dosage.

### 1. TECHNICAL DIFFICULTIES

Satisfactory results not obtained because the current is amplified million or more times and the following produce strong potential and cause artifacts.

- Movement of the electrodes
- Improper placement of the electrodes
- Mechanical defect of apparatus
- 60 cycle interference
- Muscular movements
- Movement of the patient
- Movement of the cables
- Cardiac current artifacts
- Cardiac current amplified

### USES OF ELECTROENCEPHALOGRAM IN ANESTHESIA

- During whole body perfusion to detect cerebral perfusion.
- To assess cerebral damage after anesthetic accidents (cardiac arrest).
- Detect changes in cortical activity during hypothermia.
- To detect changes in depth of anesthesia when all other methods are ineffective.
- For the use in clinical and laboratory study of new agents.



## VARIATIONS WITH INDIVIDUAL AGENTS

## I. VOLATILE ANESTHETICS

## A. Gases

*Nitrous Oxide*—70%  $N_2O$ -20%  $O_2$  produces, under pressure, wave forms of 5-7 cycles per sec. and increased amplitude. Waking frequencies replaced by slow waves 2-4 cycles per sec. and increase in amplitude up to 40 to 70 microvolts. Burst suppression not seen.

*Dinitrogen-Suppression* similar to nitrous oxide.

*Cyclopropane*—Six levels of activity. First five similar in ether. Amplitude less. Level VI absent vs. flat line results.

*Xenon*—Levels not differentiated. Total suppression not seen. Slowing of the rhythm and increased voltage. Burst suppression not seen.

## B. Liquids

*Ether*—Seven levels.

Level I—Alpha waves converted to low amplitude wave form of 80 microvolts and increased frequency 60-80 cycles per sec. (lasts 7 minutes).

Level II—Abrupt appearance of slow waves 2-3 cycles per sec. High amplitude 600-800 microvolts (lasts 60 sec.)

Level III—Rhythmicity lost. Mixed pattern appears. Slow waves with faster waves of decreased amplitude superimposed. No suppression.

Level IV—Burst suppression appears. Maximum duration 2 sec. Waves 2-4 cycles per sec. Average amplitude 150 microvolts.

Level V—Increase in suppression time 5-10 sec. Intervening wave single, smaller amplitude.

Level VI—Activity reduced to less than 1 in 10 sec. Irregular amplitude about 70 microvolts.

Level VII—Complete suppression. Activity less than 20 microvolts. Waves absent.

*Diethyl Ether* (1 barlow)—Classification of levels not available in humans.

*Fluoroethyl Ether*—Six patterns.

Pattern I—Alpha rhythm replaced by activity 12-25 cycles per sec. Voltage decreased below 25 microvolts.

Pattern II—Frequency 4-6 cycles. Low voltage up to 80 microvolts. Episodes of 6-8 sec. superimposed on fast activity of previous level.

Pattern III—Fast background activity ceases. Dominant waves increase in voltage and frequency. Regular waves 2-3 cycles. Amplitude 15-150 microvolts.

Pattern IV—Irregular large slow waves 100-800 microvolts, 2-4 cycles per sec.

Pattern V—Dominant forms fairly regular. High voltage, long duration, every 1-4 sec. Spread of 1 sec. Voltage from 100-180 microvolts. Superimposed on faster waves of 2-3 cycles per sec. in amplitude of 25-75 microvolts.

Pattern VI—Dominant slow wave frequency disappears in 1 every 8 sec. Superimposed waves of 2-3 cycles per sec. Decreased from 25 to 15 microvolts.

*Chloroform*—Six levels.

Level I—Slow frequency, higher amplitude wave pattern superimposed against fast-low amplitude background activity.

Level II—Low voltage, rapid activity.

Level III—Low voltage activity 60-80 cycles per sec.

Level IV—Delta type waves. Slow rhythm with high voltage.

Level V—60-80 cycles rhythm ends, slow waves dominant appearance.

Level VI—Decrease in amplitude of slow waves and decrease in frequency.

*Trichloroethylene with nitrous oxide*—Three levels.

Level I—Amplitude diminished from the waking tracing. Frequency increased as analgesia and unconsciousness ensue.

Level II—Rhythmic. Large, slow waves in amplitude of 100-800 microvolts, frequency 2 to 3 cycles per sec.

Level III—Frequency low, amplitude high. Rhythmicity disappears.

*Ethyl chloride*—Decreased frequency and increased amplitude.*Fluothane*—Seven levels.

Level I—The waking wave pattern changes to fast, low voltage 12-60 cycles, 10-25 microvolts.

Level II—Slow waves 2-4 cycles, amplitude 80 microvolts. Fast, low voltage activity superimposed.

Level III—Slow waves 4 cycles per sec. Amplitude 5-100 microvolts. Fast activity disappears.

Level IV—Fast activity disappears. Slow waves of amplitude 100-800 microvolts, frequency 2-3 cycles per sec. Matched and irregular.

Level V—Slow waves 1 cycle per sec., amplitude of 100-800 microvolts. Intervening smaller and faster waves in amplitude of 25-80 microvolts, frequency 2-8 cycles per sec.

Level VI—Slow wave frequency 1 cycle per 2-8 sec. Interposed and superimposed waves of 2-4 cycles, amplitude of 25 microvolts. Burst suppression appears.

Level VII—Complete suppression and absence of wave forms.

## II. NON VOLATILE DRUGS

## A. Hypnotics

*Amples Hydrate*—Decreased activity. Levels not described.

*Barbiturates*—Sedative doses no change

*Phenobarbital*—Large waves 14 cycles per sec. with sleep. Burst suppression with narcosis.

*Thiopental*—Five levels.

Level I—High amplitude 75-80 microvolts, fast frequency 10-20 cycles per sec. spiky

Level II—Complex. Slow waves, irregular contour, random occurrence of frequency from 8 cycles upward, amplitude up to 180 microvolts. "Spiky" waves with irregular amplitude and frequencies of 10 cycles superimposed on slow waves.

Level III—Suppression less than 3 sec. duration. Biphasic bursts. First phase 1 sec. frequency 10 cycles. Second phase 8 cycles emerging into next suppression.

Level IV—Marked suppression 8-10 sec. Activity similar to III but less amplitude.

Level V—Activity every 10 sec., amplitude less than 65 microvolts.

*Hypnotics (1 sec.)*—Four levels.

Level I—Suppresses alpha activity. Slow waves 4-8 cycles per sec. Increased amplitude.

Level II—Complex pattern 8-10 cycles per sec. Amplitude 6-100 microvolts. Superimposed low fast activity with spiky effect.

Level III—Burst suppression several sec. duration.

Level IV—Widely spaced burst of activity of less than 20 microvolts, appearing in flat tracing.

## B. Narcotics

*Morphine*—No significant effect. Analgesic doses.

*Methadon*—Analgesic doses no effect

*Meprobamate*—No effect

*Chlorpromazine*—(45 mg.) P. activity induced by intravenous injection. Oral no effect. Decreased amount of ether necessary for Level IV

## C. Anesthetics

*Ethynol*—Reverts pattern produced by barbiturates to wider patterns of light narcosis. Alone similar effects as a convulsant.

*Levodopa*—Further slowing of frequencies when used with  $\text{NaO}$  and meprobamate. No reversal of cortical patterns.

*Cocaine*—No effects

## D. Muscle Relaxants

*Curare*—No effects.

*Erythrol*—No effects.

*Gallamine (Flaxedil)*—No effects.

*Dactinomycin*—No effects.

*Succinyl Choline*—No effects.

## E. Miscellaneous Drugs

*Ergotamine*—No effects.

*Flunitrazepam*—No effects.

*Fluparone (Pitavrin)*—No effects.

*Sodium Nitrite*—No effects.

*Phenylephrine (Neosynephrine)*—No effects.

*Ephedrine*—No effects.

## F. Premedication

*Atrypine*—1/100-1/150 grain I.V. causes decrease in voltage of all waves, followed by bursts of high voltage waves with 10 cycles per sec. Bursts appear at 10 sec. intervals, last 1-3 sec.

## G. Anoxia—Electroencephalograph useful for detecting anoxia particularly for extracorporeal perfusion. Changes significant. Tracings of prognostic value.

*Isobaric Anoxia*—Increase in rate and of amplitude of waves followed by pronounced slowing. Great increase in amplitude. Finally decline to a flat tracing.

*Segment Anoxia*—Same as anoxic. Inhalation of 6-11% oxygen. Small, fast activity within 60 seconds replaced by slow large waves. Recovery in reverse order.

## H. Hypotension—Inadequate cerebral perfusion results in changes characteristic of anoxia. Depression of high voltage, fast activity as pressure declines. Cortical activity ceases at levels 80 mm Hg. Vasopressors restore rhythm toward normal.

## I. Hypothermia—Usually negligible change. Tendency towards slowing of frequency not greater than 25%. Occlusion of circulation results in superimposed low voltage, fast frequency activity developed and persisted after cessation of lower frequencies. Becomes isoelectric for duration of occlusion. After release activity reappears and gradually returns to pre-occlusion level. Low voltage, fast frequency activity (8-16 pattern) occurs during recovery from occlusion.

## J. Hypoglycemia—Decrease in alpha activity reversible with ingestion of sugar. Insulin coma causes abrupt appearance of large, slow waves as consciousness is lost. Severe hypoglycemia abolishes cortical activity.

## K. Hyperventilation—No change.

## DELIBERATELY INDUCED HYPOTENSION DURING ANESTHESIA AND OPERATION

**SYNONYMS**—Controlled hypotension Hypotensive anesthesia purposefully induced hypotension

**DEFINITION**—Deliberate induction of a disparity between the circulating blood volume and the size of the vascular bed. Accomplished by (1) decreasing the blood volume or (2) relaxing vascular bed by decreasing peripheral resistance by denervation of vascular innervation by blockade or chemical agents.

**RATIONAL**—Tolerance to hypotension due to blood loss appears to be greater in subjects with decreased peripheral resistance. Onset of irreversible shock delayed. Normal capillary pressure remains unchanged—32 mm. Hg. Reduction in peripheral resistance favors maintenance of normal capillary pressure and permits blood to flow even though systolic blood pressure is reduced. Perfusion remains adequate.

**HISTORY**—Morton (England) 1900 used total spinal block for operation. Alao Koester (1925) Jonnesco, Holmlundt and Page used it experimentally to study shock in surgical procedures. First used by Gardner and Hale (CfRe Clinic) 1940 by technique of arteriotomy. Total spinal techniques first used by Gillis (England) 1948. Davison and Elderly (England) 1950 used hexamethonium and Nicholson, Sarnoff and Crehan (Boston) used thiophanum (Arfonad) for ganglionic blockade. Bromage Hingston advocated use of peridural block. Phenister first demonstrated benefit of vascular denervation in rabbits.

### INDICATIONS SURGICAL

- (1) To obtain "dry field."
- (2) Conserve blood (rare types)
- (3) Reduce organ tension (brain, liver, kidney)
- (4) Avoid transfusions.
- (5) Reduction of intravascular tension.
- (6) Control of hypertensive crises.
- (7) Attenuation of autonomic stimuli.

### INDICATIONS MEDICAL

- (1) Combat pulmonary edema.
- (2) Decrease cardiovascular bleeding.
- (3) Decrease venous congestion in cardiac failure.
- (4) To decrease sympathetic over-activity.
- (5) To combat pain due to vasospasm.

### SITES OF VASCULAR DENERVATION AND METHODS OF REDUCING BLOOD VOLUME AND PERIPHERAL RESISTANCE

**Autonomic Centers**—Depression of vasomotor impulses from autonomic centers in midbrain and thalamus. Hydralazine (Apressoline) believed to act at this site. Not practical for use during operation.

**Autonomic Ganglia**—Chemical blockade by systemic use of hexamethonium, pendamine, thiophanum (Arfonad). Feasible and technique of choice for operation.

### Medullary Centers

- (a) **Locus Coeruleus**—Depressed by excess of narcotics (morphine) basal hypotensives (barbiturates) or anesthetics. Not practical—respiratory and other vital centers depressed simultaneously.
- (b) **Vasomotor Center**—Stimulated—increasing number of dilator impulses. Veratrum alkaloids act in this manner. Not practical for use during anesthesia.

**Adrenergic Receptors**—Blockade of sympathetic efferent cells by sympatholytic and adrenergic drugs—epinephrine, procaine, phenothiazine derivatives. Blockade difficult to reverse with adrenaline because of persistent blockade. Not controllable.

**Arterial Smooth Muscle**—Depression by nitrites, local anesthetics and other smooth muscle depressants. Not practical. Not readily controllable with variable agents.

**Capillaries**—Increase in permeability causes fluid to be lost from vascular space into extravascular space (Hitzman)—Not controllable, reversible or practical.

**Heart**—Depress myocardium and reduce cardiac output (15-20%). Vasoconstriction present. Perfusion inadequate in peripheral vessels.

**Intervertebral Foramen**—Blockade of sympathetic preganglionic with a local anesthetic as they emerge from the cord by ( ) total at block, (b) epidural block, (c) sympathetic ganglion block. Total at or epidural block feasible and used. Sympathetic ganglion block practical.

### UNCHANGED INITIALLY BY BLOCKADE, DECREASED LATE

**Blood Volume**—Decreased by withdrawal of blood from radial (artery). Objectionable because sensation remains intact and induces vasoconstriction. May lapse into irreversible shock.



## PHYSIOLOGICAL CHANGES DURING DELIBERATELY INDUCED HYPOTENSION

**Brain**—Cortex depressed. Psychometric tests indicate cerebral changes postoperatively. Quantity of anesthetic reduced as blood pressure falls. Cerebral oxygen consumption unchanged (unanesthetized). Decreases with anesthesia. A.V. difference widened. Intracranial pressure reduced. Brain volume decreased (arteriotomy). Cerebral blood flow decreased. Decreased still more with head-up tilting. Cerebral congestion with head-down tilting. Cerebral damage favored by head-up position.

E.E.G. shows suppression suggestive of anoxia. Depression of high voltage fast activity as pressure decreases. Ceases at 80 mm. Hg. Use of vasopressors restores to nonanesthetic state and return of activity 1 normal.

**Vagus**—Active during spinal and epidural block. Ganglionic blockade prevents transmission of impulses.

**Metabolism**—Oxygen consumption decreased 33% or more. Neuroleptic drugs metabolized more slowly during and after hypotension.

**Lung**—Ventilation decreased. Arterial blood oxygen unchanged.  $CO_2$  tension variable. Tends to increase. Total  $CO_2$  content increases.  $CO_2$  combining power decreased.

**Breasts**—Increased tone—spasm possible (spinal and peridural).

**Liver**—Bile excretion impaired for as long as 7 days. Overall liver dysfunction enhanced.

**Kidney**—Renal blood flow and filtration rate depressed. Filtration decreased. Urinary output decreased. Varies with degree of hypotension. Anuria follows if systolic less than 60 mm. Hg is sustained. Clearance of drug decreased during hypotension. Drugs tend to accumulate. Renal dysfunction in post-operative period common. Excretion rate of sodium and water prolonged. Filtration rate remains depressed, even though function is restored to normal if hypotension exists for more than 3 hours.

**Blood**—Volume unchanged during blockade unless prolonged. Decreased with arteriotomy. Plasma volume reduced if progresses into irreversible shock. Blood sugar decreased.

**Eyes**—Pupils dilate. Accommodation lost. Blurred vision due to effect of drug. Blindness postoperatively due to anoxia, mask pressure, or thrombosis of retinal artery.

**Salivary Glands**—Secretions decreased.

**Trachea**—Slosh of mucus may occur due to pressure from intratracheal cuff.

**Heart**—Depression of myocardium decreases contractile force and mean arterial pressure. Coronary blood flow decreases. E.K.G. changes suggestive of infarct (ischemia). Stroke volume decreased due to activation of Bainbridge reflex (spinal). Pulse increased with ganglionic blockade (vagi blocked). Stroke volume compensated for.

**Venous Pressure**—Right auricular pressure decreased. Peripheral venous pressure increased. Venous return to heart markedly decreased.

**Blood Pressure**—Pulse pressure decreased. Diastolic pressure reduced due to decreased peripheral resistance. Systolic cannot be reduced to 80 mm. Hg to effectively block ocs (both spinal and ganglionic blockade). Blood pressure not changed (early) with arteriotomy. Postural changes: Decreases with head up tilt, increases with head-down tilt.

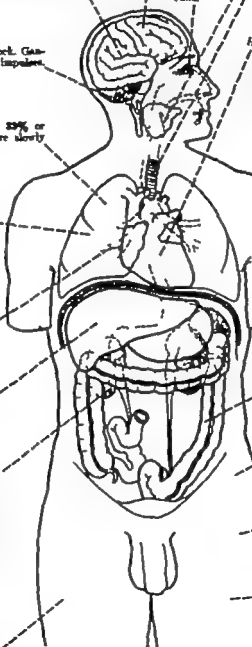
**Gastro-Intestinal**—Gastric secretions decreased. Bowel constricted (spinal). Dilated (viscous blockade).

**Circulation Time**—Prolonged. May be doubled. Blood flow decreased. A.V. difference widened (spinal, epidural and systemic diversion).

**Arterioles and Capillaries**—Capillary pressure not decreased. Arterioles relaxed (except in arteriotomy—constricted). Oozing decreases. Sympathetic blood flow decreased. Digital blood flow increased.

**Limbs**—Negative pressure applied to extremity with plethysmograph. F ven dilation of vessels and pooling of blood in extremity. Not practical.

**Skin**—Temperature decreased due to vasodilation. Blood flow increased. Sweating absent. Slosh may occur from pressure due to strips, retractors, etc.



## CONTRAINDICATIONS

- (1) Arteriosclerosis of major vessels.
- (2) Essential hypertension.
- (3) Essential hypotension, or shock from any cause.
- (4) Hyperolemia.
- (5) Asepsia.
- (6) Impaired renal function.
- (7) Liver dysfunction.
- (8) Cardiac disease with impaired myocardial function.
- (9) Polycythemia—thrombi may result.
- (10) Adrenal deficiency.

## COMPLICATIONS AND SEQUELAE

- (1) Hemorrhage postoperatively due to inadequate hemostasis.
- (2) Prolonged cerebral depression postoperatively (anoxia).
- (3) Cerebral damage due to inadequate perfusion.
- (4) Thrombosis of major vessels, particularly the cerebral, coronary.
- (5) Oliguria and anuria.
- (6) Asystole due to inadequate perfusion.

## DISADVANTAGES AND OBJECTIONS

- (1) Circulation time prolonged causing A.V. difference to be widened—tissue anoxia may result.
- (2) Irreversible shock may develop.
- (3) Responses to desaturation unpredictable. Vary from patient to patient.

## TYPES OF SURGERY FOR WHICH EMPLOYED

- (1) Neurosurgery
- (2) Radical surgery for malignant disease
- (3) Fenestration, neurectomy and other procedure requiring a dry field for success.

## DRUGS USED

Trimethoprim. Camphorsulphonate (Arimad)—0.1-0.2 mgm. per pound. Administered as continuous intravenous drip composed of 1 mgm. per cc. Administered over a period of 10 minutes until blood pressure is reduced to 80 mm. Hg and then adjusted to drip at rate to maintain tension at desired level.

Proxymethonium and Hexamethonium—Hexamethonium preferred. Dose varies from 2-44 mgm. intravenously in fractions. Both drugs characterized by tachyphylaxis. Prolonged effect in some patients. Difficult to reverse.

Anesthetic Technique—"Controlled" hypotension may be induced during any type of anesthesia—nitrous oxide-ether, nitrous oxide-thiopental, succinyl choline, cyclopropane, cyclopropane-ether, etc.

## ADVANTAGES OF GANGLIONIC BLOCKADE OVER OTHER METHODS

- (1) Greater controllability
- (2) Reversal possible with ephedrine, phenylephrine and other vaso-pressors. Response to adrenergic substances remains intact.
- (3) May be interrupted with greater ease (with short-acting drugs)

## ARTERIOTOMY

Description—Blood drawn from radial artery into sterile receptacle with heparin. Re-infused later. Oozing diminished by vasoconstrictor.

## Objections

- (1) Peripheral resistance increased. N. vascular denervation
- (2) Irreversible shock may occur
- (3) Artery sacrificed—gangrene of hand possible.
- (4) Blood cannot be re-infused in toto due to contracted vascular bed.
- (5) Relatively complicated and time consuming.

## PRECAUTIONS

- (1) Limit period of hypotension to one hour or less—irreversible shock may develop otherwise.
- (2) Avoid pressure on exposed parts of body—necrosis may develop.
- (3) Induce and maintain hypotension until need for it is no longer present (tachyphylaxis to drug may develop—subsequent doses without effect)
- (4) Restore blood pressure to non-operative level at conclusion of operation—visualize bleeding points.
- (5) Replace blood as lost.

## HYPOTHERMIA

**HISTORY**—First observed by Walther in rabbits in 1892. Reported by Britton in 1922. Temple Fay (Philadelphia) cooled narcotized patients for treatment of cancer. McQuiston advocated cooling during surgery in 1947. James Arnolt (Aberdeen, 1847) used cooling for surgery.

## DEFINITIONS

**TOTAL BODY HYPOTHERMIA**—The deliberate reduction of total body temperature accomplished by inactivation of the heat regulating temperature by a central nervous system depressant (any volatile anesthetic or non-volatile basal narcotic) and exposing the body to cold environment (water bath, cold air, etc.) just above freezing temperature. Used for reducing general metabolism of the tissues. Inactivation of heat control mechanisms converts the subject from a homothermal one to a poikilothermal.

**HIBERNATION**—The voluntary inactivation of the heat regulating center by an animal endowed with this ability so that body temperature may be reduced to decrease metabolism. This inactivation is quickly and voluntarily reversible.

**ARTIFICIAL HIBERNATION**—The inactivation of the heat regulating center in a non-hibernating animal by drugs (phenothiazines) and reduction in body temperature by loss of heat to the environment. Temperature reduction comparatively slight. Non-reversible by the animal.

**REGIONAL COOLING**—The cooling to low temperatures of an organ (brain) vulnerable to ischemia during occlusion of the circulation by cooling blood entering that organ.

**HYPERTHERMIC ANESTHESIA**—The regional cooling of a limb by occluding the blood supply and surrounding limb in ice. Designed to obtain anesthesia by cold. Used for "physiological" amputation.

## PURPOSES OF TOTAL BODY COOLING

- (1) Reduces metabolism of tissues in procedure in which ischemia is anticipated.
- (2) Reduces cerebral volume in neurosurgical procedures.
- (3) Reduces body temperature in hyperpyrexia.
- (4) Reduces blood pressure—possibly protects against hemorrhagic shock.

4. Air cooling by placing cold air in chamber
  - (a) Conbersome
  - (b) Slow
  - (c) Feasible most common by this method

5. Flural peritoneal perfusion with saline.
  - (a) Slow
  - (b) Conbersome
  - (c) Awkward
  - (d) Large volumes of solutions needed

## DISADVANTAGES AND HAZARDS

1. Cardiac irritability increased. Irreversible ventricular fibrillation may occur.
2. Respiratory alkalosis occurs.
3. Uncontrollable lag may cause cooling to lethal range.
4. Tissue damage may occur from pressure, freezing with supercooled ice or heat on re-warming.
5. Re-warming slow and difficult.
6. Depression of circulatory system persists beyond restoration of normal temperature.
7. Heat regulatory mechanism remains unstable for periods of time after re-warming.
8. Concomitant awkward, time-consuming.
9. Reactionary hemorrhage may occur postoperatively.

6. Gastric or colonic lavage with ice water
  - (a) Conbersome
  - (b) Not controllable

7. Removing blood cooling and returning to body
  - (a) Complicated
  - (b) Not readily reliable
  - (c) Contamination possible
  - (d) Hemolysis

8. Use of drugs alone (phenothiazines)
  - (a) Temperature falls slowly
  - (b) Not controllable
  - (c) Extreme low temperatures not obtainable

9. Regional cooling. Extremity packed in ice for 2-3 hours. Used for hypothermic anesthesia for surgical procedures or to reduce metabolism in limb.

## METHODS OF COOLING

1. Total body immersion in cold water
  - (a) Cooling uniform and rapid
  - (b) Least controllable, cumbersome
  - (c) Cooling must be accomplished before patient is positioned.
2. Application of wet packs
  - (a) Slow but most controllable
  - (b) Least reliable
  - (c) Fat necrosis reported must often with this
3. Surrounding body with blankets containing coils through which ice water flows
  - (a) Slow
  - (b) Slow burns on re-warming
  - (c) Reasonably controllable

## REWARMING

Spontaneous rewarming occurs at 1°C. per hour average. Reflexes appear at 31°C.—consciousness at 32°C. Quicker with surface warming. Temperature may overshoot and continue to rise above normal.

Cardiac output fails to return to normal after rewarming. Blood pressure rises to normal at normothermia. Circulatory derangements & overheat the longer period of cooling. Tend to become resistant with rewarming.

**Cerebrum**—Planes and stages of Guedel qualified below 30°C. Loss of consciousness at 29°C. Returns at 34-34° (without anesthesia). Below 28°C. no anesthetic agent is required. E.E.G. shows progressive decrease of activity.

**Heat Regulating Center**—Must be inactivated by drugs to produce cooling. Hibernating animals voluntarily return center to activity. Non-hibernating animals unable to do so.

**Respiratory Center**—Depressed. Inactivated at 28°C. Artificial respiration required. Thoracic cavity respiratory arrest before circulatory. Either stimulates locally. Apnea does not result before cardiac arrest.

**Cardiac Body**—Activity decreased.

**Lungs**—Respiratory rate slowed. Deflation and inflation prolonged and more difficult as cooling progresses. Quantities of gases dissolved in blood increases as temperature is lowered. Dissolved CO<sub>2</sub> increased causing alkalosis. Hyperventilation may cause alkalosis. Sudden release of CO<sub>2</sub> may predispose to ventricular fibrillation.

**Metabolism**—Heat output decreases 80 cal/mq. mm. body surface 37°C to 10-15°C. at 28°C. Oxygen consumption decreased. Increased in shivering. Nor-mal metabolic process requires 4% oxygen from inspired air. Hypothermia at 28° about 4%.

**Liver**—Chemical reactions slowed. Reduced activity of enzymes. Hepatoxic effect of some drugs enhanced (vinyl ether). Drugs slowly metabolized. Onset and duration may be prolonged.

**Adrenals**—Cortisol output decreased. Response to surgery delayed and diminished but not completely suppressed. Secretion of epinephrine and norepinephrine reduced. Adrenal response to A.C.T.H. not decreased. Glomerular filtration and renal blood flow decreased.

**Kidneys**—Decrease in urinary output which is proportional to decrease in blood flow. Returns to normal at normothermia. Does not prevent renal damage from ischemia of kidney caused by occluding renal artery. Distal tubular function reduced and eliminated at 28°C. Proximal tubular activity little affected.

**Deep Reflexes**—Disappear at 28°C., reappear at 31°C.

**Muscles**—Usually spastic in action. Responds to relaxants. Shivering occurs in surface cooling when nervous is insufficient to depress heat regulating center. Increases oxygen consumption 400% and cardiac activity.

**Nervous Conduction**—Decreased below 28°C and ceases at 4°C.

**Body Temperature**—Continues to drift after surface cooling is terminated.

**Antemortem Post-mortem**—Vermis possible at site of pressure due to straps, restraints, etc. Adipose tissue tends to solidify. Children have it more than adults. More elastic in adult (liquid) than newborn. More palmar (solid) to newborn.

**Cerebrospinal Fluid Pressure**—Falls with body temperature. Rises during induction of anesthesia, intubation or during shivering.

**Eyes**—Pupils dilated. Ability to perceive light disappears at 27°C. Corneal reflex disappears at 31°C.

**Ears**—Hearing disappears at 27°C. Control of equilibrium disappears at approximately 27°C.

**Pharynx**—Pharyngeal reflex obliterated below 28°C.

**Larynx**—Necrosis of mucous membrane may result from pressure of cuffed intratracheal tube. Reflex abolished below 28°C.

**Heart**—Rate decreases. Cardiac output decreased at 30°C at 25°C. Systolic time increased. Time for isometric relaxation increased. Heart contracts and relaxes with more completeness. Cooling inhibits aerobic oxidation of metabolites. Cardiac irritability increased progressively as temperature falls. Ventricular fibrillation occurs at 25-30°C. Electric defibrillation difficult without rewarmed. Fibrillation initiated by mechanical stimulation. Not precipitated by over load. Sudden increase in pH from rapid relief of acidosis may cause ventricular fibrillation. Coronary blood flow not decreased.

**Circulation Time**—Prolonged, almost doubled.

**Blood Pressure**—Difficult to determine by usual techniques due to intense vasoconstriction. Decreases progressively with cooling. Returns to normal with rewarming.

**Venous Pressure**—Variable. Decreases after rewarming.

**Peripheral Resistance**—Increased up to 35%. Use of general anesthesia tends to decrease vasoconstriction.

**Oesophagus**—Oesophageal temperatures more accurate index of cardiac temperature than rectal.

**Blood Volume**—Decreased. Plasma volume decreased by translocation of fluid into tissue spaces.

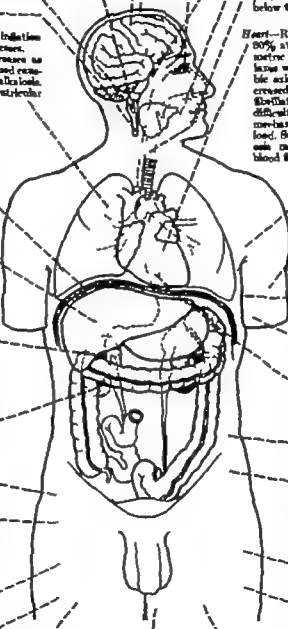
**Blood Viscosity**—Increased. Thrombocytopenia and an increase in W.B.C. during increase in W.B.C. after and hemorrhage of magnitude tolerated during normothermia may be fatal. Eosinophils increase. Replace blood as it is lost.

**Bleeding Time**—Prolonged. Decrease in platelets may be factor.

**Clotting Time**—Prolonged. Alterations in fibrinogen content may be factor.

**Plasma Volume**—Diminished about 10%. Plasma trapped in some of small vessels. Plasma protein not changed.

**Skin**—Cherry red color during—pale during re-warming—lips and mucous membranes blue. Necrosis may occur due to pressure on ischemic areas. Freezing point—-6-1°C.





## COMPLICATIONS AND ACCIDENTS DURING ANESTHESIA

**Cerebral Anoxia**—Cause not definitely established. May accompany anoxia,  $\text{CO}_2$  excess or both, or follow accidental intravenous administration or overdosage of local anesthetic. Idiopathic type usually occurs if fever, acidosis, and particularly if  $\text{CO}_2$  excess are present. Cause not known—many theories to explain it—pyrexia, increased cerebral vascularity, hyperkalemia, hypoglycemia, ketosis, atropine overdosage, alkalosis, isopentanes in drugs, cerebral edema, asphyxia, neurotoxicity, etc. None proved. May be due to direct stimulation of motor centers by drug (vinethene).

**"Cerebral Anoxia"**—Signs variable: unequal pupils and flaccid paralysis most common symptoms. Anoxia or hypercapnia may precipitate in hypersensitive subjects.

**Prolonged Second Stage**—Unsatisfactory preoxygenation, chronic alcoholism, respiratory obstruction.

**Vagal Reflexes**—Elicited by stimulation of bilus of lung, trachea or esophagus. Results in poor, cardiac rhythmias and hyper or hypotension.

**Asphyxia**—Occurs during induction or maintenance if patient passes into stage II. Full stomach and changes of position predispose.

**Regurgitation**—Occurs during deep anesthesia. Common when gastric dilatation or intestinal obstruction is present. May cause drowning.

**"Dead g"**—Worm cramps, respiratory obstruction, prolonged ether anesthesia.

**Dilated Pupil**—Overdosage of anesthetic drug, anoxia, excessive atropine or acepromazine.

**Unequal P. pupils**—Undetermined, sign of cerebrovascular accident.

**Salivation**—Preoxygenation administered too early, late or insufficient in quantity.

**Bluish Lymphatics**—Sudden death of unknown origin: subjects have hyperplasia of lymphoid tissue or enlarged thymus seen in young subjects.

**Tachycardia**—Shock, blood loss, excessive atropine or partial respiratory obstruction may be cause.

**Bradycardia**—Usually caused by drug, anoxia or heart block due to pre-existing disease.

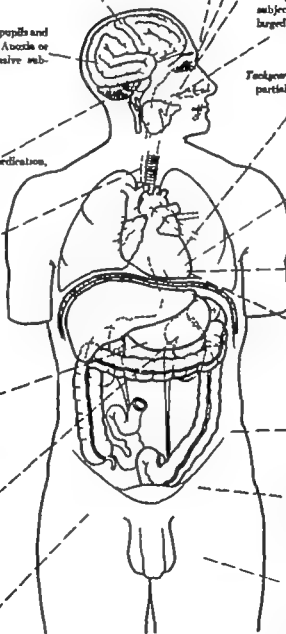
**Arrhythmias**—May occur with all types of agents and procedures. Most frequent with cyclopropane and chloroform; may decrease cardiac output which predisposes to cardiac failure.

**Contracture Fibrillation**—Results from increased cardiac irritability induced by agents such as cyclopropane. Increased sympathetic activity and adrenergic output may enhance irritability.

**Apnoea**—Anoxia, overdosage with failure to revive or vagal reflexes.

**Hypertension**—Follows spinal anesthesia, blood loss, trauma, reflex stimulation, postural changes, overdosage (increased blood).

**Hypertension**—May be caused by hyperventilation (from exhausted soda lime; large dead space or added  $\text{CO}_2$ ), opposite effect of anesthetic agent; vasoconstrictor drug (a local anesthetic solution). Reflex stimulation, or excitement during induction.



**Respiratory Failure**—May be caused by overdose of agent, over-pneumatization, central effect of anoxia on medullary centers; paralysis from overdose of local anesthetic. May follow circulatory failure from shock due to trauma, blood loss or neurogenic origin.

**Apnea**—May be caused by:

- (1) Oxygenation and removal of anoxic stimulation of carotid body in cases of respiratory depression from overoxygenation.
- (2) Overdistention of alveoli from positive pressure
- (3) An apprehensive subject may hyperventilate during second stage causing apnea or combination of all three factors. Increased intra-cranial pressure or reflex stimulation of pericardium, pleura, peritoneum or bronchi stimulation of Hering-Breuer reflex may cause it. (Overdosage excepted.)

**Hyperventilation**—Hyperventilation due to local alveolar stimulation caused by agent, awkward position, or other compressive response to hyperventilation.

**Dyspnea**—Anoxia,  $\text{CO}_2$  excess, awkward position, central depression of respiratory center.

**Emboli**—

- (1) Air—not related to anesthesia may occur in thoracic surgery or when large veins are opened (place head below shoulders)
- (2) Fat—even after manipulations of transfused large bones after 24 to 36 days
- (3) Tree emboli—normal due to clots being dislodged and carried to pulmonary vessels.

**Epistaxis**—Trauma from nasal airways is most frequent cause

**Aspiration**—The presence of vomitus, blood, pus, lymphoid tissue instruments, loose teeth, etc. in the airway may lodge in trachea and bronchi. Secretions or blood in thoracic surgery passers from pathological secretions portion to healthy portion.

**Obstruction**—Due to relaxation of tongue, pharyngeal muscles, secretions, compression of airway tumor masses, laryngeal spasm, etc.

**Tracheal Collapse**—Occurs in pathological states of trachea in which tracheal cartilages are eroded or thinned.

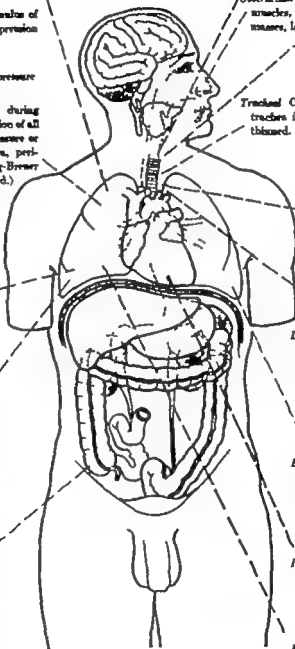
**Curling**—Occurs during light anesthesia, also following intubation. Abdominal contents may be pushed outward causing technical difficulties. May be induced by hilar stimulation.

**Laryngeal Spasm**—Due to many causes— $\text{CO}_2$  excess, excessive secretions or canister dirt, reflex stimulation, high concentration of agent, manipulations with laryngoscope central stimulation (cyclo or pentathal).

**Bronchospasm**—Presence of catheter in trachea. Central effect of agent, histamine-like action (of curare) hilar stimulation

**Hiccups**—May follow manipulation of phrenic nerve diaphragm or  $\text{CO}_2$  excess

**Pulmonary Edema**—Caused by cardiac decompensation during anesthesia. May be initiated by Trendelenburg position in impending cardiac decompensation or cardiac failure from shock or overdosage, or excessive administration of fluid.



## COMPLICATIONS AND ACCIDENTS DURING ANESTHESIA

**Coronary**—Causes not definitely established. May accompany noxia, CO<sub>2</sub> excess or both, or follow accidental intravenous administration or overdosage of local anesthetic. Idiopathic type usually occurs 1/2 fever, acidosis, and particularly if CO<sub>2</sub> curves are present. Cause not known—many theories to explain it—pyrexia, increased cerebral vascularity, hypoxiaemia, hypervolemia, ketosis, atropine overdosage, alkalosis, hyperkalemia in drugs, cerebral edema, asphyxia, neuroleptosis, etc. None proved. May be due to direct stimulation of motor centers by drug (vibrations).

**Dilated P. pupil**—Overdosage of anesthetic drug, anoxia, excessive atropine or scopolamine.

**Unequal Pupils**—Undetermined; sign of cerebrovascular accident.

**Salivation**—Pneumothorax administered too early, late or insufficient in quantity.

**Stasis Lymphaticus**—Sudden death of unknown origin, subjects have hyperplasia of thymoid tissue or enlarged thymus; seen in young subjects.

**"Cerebral Accident"**—Sign variable; unequal pupils and flaccid paralysis most common symptoms. Anoxia or hypercapnia may precipitate in hypertensive subjects.

**Paroxysms**—Shock, blood loss, excessive atropine or partial respiratory obstruction may be cause.

**Prolonged Second Stage**—Insufficient premedication, chronic alcoholism, respiratory obstruction.

**Bradycardia**—Usually caused by drug, noxia or heart block due to pre-existing disease.

**Laryngeal Reflexes**—Elicited by stimulation of larynx, trachea or esophagus. Results in spasm, cardiac arrhythmias and hyper or hypotension.

**Arrhythmias**—May occur with all types of agents and procedures. Most frequent with cyclopropane and chloroform may decrease cardiac output which predisposes to cardiac failure.

**Forceful ejection**—Occurs during induction or maintenance of patient's present stage. If full stomach and change of position predispose.

**Ventricular Fibrillation**—Results from increased cardiac irritability induced by agents such as cyclopropane. Increased vagathetic activity and adrenergic output may enhance irritability.

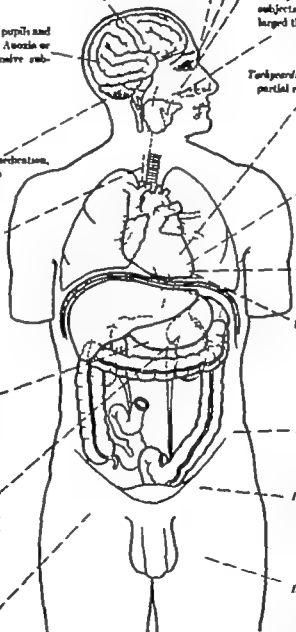
**Hyperpnea**—Occurs during deep anesthesia. Common when gastric dilatation or intubation of trachea are present. May cause drowning.

**Apnoea**—Anoxia, overdosage with failure to revive or vagal reflexes.

**Hypertension**—Follows spinal anesthesia, blood loss, trauma, reflex stimulation, postural changes, overdosage incompatible blood.

**Smoking**—If no environment, respiratory obstruction, prolonged ether anesthesia.

**Hypotension**—May be caused by hyperpnea (from exhausted acids), large dead space or added CO<sub>2</sub>, asphyxial effect of anesthetic agent, vasomotor drug in local anesthetic solutions, reflex stimulation, or vasodilation during induction.



**Respiratory Failure**—May be caused by overdose of agent, over-premedication, central effect of noxia on medullary center: paralysis from overdose of local anesthetic. May follow circulatory failure from shock due to trauma, blood loss or neurogenic origin.

**Apnea**—May be caused by

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**Hypoxia**—Hypoxia due to local alveolar stimulation caused by agent, awkward position, or other compensatory response to hyperventilation.

**Dyspnea**—Anoxia, CO<sub>2</sub> excess, awkward position, central depression of respiratory center.

**Emboli**—

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- (3) True emboli—arterial due to clots being dislodged and carried to pulmonary vessels.

**Epiatosis**—Trauma from nasal airway is most frequent cause

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**Obstruction**—Due to relaxation of tongue, pharyngeal muscles, secretions, compression of airway tumor masses, laryngeal spasm, etc.

**Tracheal Collapse**—Occurs in pathological states of trachea in which tracheal cartilages are eroded or thinned.

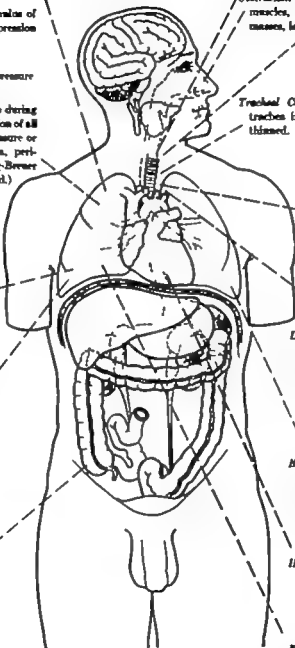
**Coughing**—Occurs during light anesthesia, also following intubation. Abdominal contents may be pushed outward causing technical difficulties. May be induced by hilar stimulation

**Laryngeal Spasm**—Due to many causes—CO<sub>2</sub> excess, excessive secretions or canister dirt, reflex stimulation, high concentration of agent, manipulations with laryngoscope, central stimulation (cyclic or peritoeal)

**Brachial palsy**—Presence of catheter in trachea. Central effect of agent, Metaxalone-like action (of curare), hilar stimulation.

**Hiccups**—May follow manipulations of phrenic nerve, diaphragm or CO<sub>2</sub> excess.

**Pulmonary Edema**—Caused by cardiac decompensation during anesthesia. May be initiated by Trendelenburg position in impending cardiac decompensation or cardiac failure from shock or overdosage, or excessive administration of fluid.



## POST ANESTHETIC SEQUELAE

**Cerebral Center**—May be depressed by excess of non-volatile drugs.

**Center**—Damage from anoxia or hypervoxia during anesthesia may cause twitchings, convulsions or other neuromuscular symptoms. Coma and death may follow severe cases.

**Respiratory Center**—May be depressed by non-volatile drugs administered in excess or from cumulative action.

**Eye**—Conjunctivitis caused by allowing ether and other volatile liquids or secretions to pass into the eye.

**Facial Center**—Emesis and nausea common. May be due to anoxia during anesthesia, effect of agent, circulatory disturbances or surgical manipulations.

**Trachea**—Tracheitis usually follows intubation.

**Lungs**—Atelectasis may follow within first 48 hours. Relationship to anoxia not established. Broncho-pneumonia may follow aspiration. Lung abscess may follow aspiration. Emboli (air fat or clot) may occur. Not related to anesthesia. Pulmonary edema may occur. Relationship to anesthesia doubtful.

**Pharynx**—Pharyngitis may follow trauma caused by airway or suction tips.

**Diaphragm**—Pneumothorax may occur. Relationship to anesthesia not established.

**Heart**—Anesthetics rarely cause any notable effects after withdrawal of drug.

**Liver**—Hepatitis follows use of halogenated hydrocarbons in small percentage of cases. Latent period precedes onset of condition.

**Stomach**—Gastritis may follow use of irritating drugs. Gastric distention may occur. Relationship to anesthesia not known.

**Kidney**—Renal damage uncommon. Hematuria is not observed. Oliguria frequent. Anuria not common.

**Intestine**—Intestinal and renal blood may occur. May be caused by anesthetic partly and postoperative isolation.

**Bladder**—Urinary and urinary retention frequent.

**Vagina**—Thrombosis follows intravenous administration of concentrated solutions.

**Proctum**—Caused by irritation from systemic, rectal ether and other rectal anesthetics.

**Blood**—Hemoconcentration frequent from dehydration or shock. Anoxia and hypervoxia may occur from anesthesia when metabolic disturbances and renal diseases are present.

**Nose**—Frorescence may follow coughing from respiratory complications.

**Extremities**—Gangrene may be caused by use of vasoconstrictors with local anesthetics in vasoconstrictor chambers. Also use of highly concentrated solution of drugs.

**Mouth**—Ulcers. Rarely caused by trauma from upward withdrawal of drug.

**Body Temperature**—If pyrexia results from cerebral damage from anoxia, heat stroke or embolism cause.

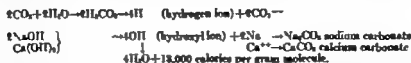
**Nerve**—Palsies may follow spinal anesthesia, particularly 6th and 8th nerves.

Also irritating drugs produce erythema. Rash often follows use of non-volatile drugs. Vasoconstriction may occur after forced ventilation of lung or after expiration, due to trauma of respiratory tract. Sore throat may follow use of locally irritating anesthetic drugs, only when oral or extravascular use of local anesthetic.

## THE CHEMICAL ABSORPTION OF CARBON DIOXIDE

**HISTORY**—First applied to anesthesia by Dennis Jackson in 1913 on animals, also in man (St. Louis, Mo.) in a few clinical trials. Ralph M. Waters introduced "to and fro" filter in 1923 Brian Sword and Richard Von Foregger introduced "circle filter" in 1926 Benedict in 1909 used soda lime for carbon dioxide absorption in studies on metabolism. Wilson and Dewey developed granulated soda lime for use in inhaler in 1919.

**PRINCIPLE**—The exhaled atmosphere containing carbon dioxide is passed through a filter containing alkaline substances. Carbonic acid forms from interaction of carbon dioxide and water which is in turn neutralized by the alkali to form carbonates, water and heat.



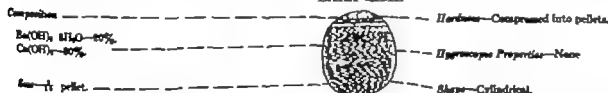
**ABSORBENTS**—Two absorbents are in current use—soda lime and bara lime (baralyne). Soda lime for anesthesia is a specially prepared mixture of sodium and calcium hydroxides to conform to requirements of hardness, size and porosity and moisture content for clinical use. Specimens vary according to manufacturers. Bara lime is composed of barium and calcium hydroxide. Soda lime for anesthesia possesses the following features:

## SODA LIME



The sodium hydroxide is the more active of the two bases. It imparts greater efficiency to the mixture than would be possessed by the lime alone. The bulk of the absorption is carried out by the calcium hydroxide. One pound absorbs for six hours intermittent use at 600 cc. CO<sub>2</sub> output per minute.

## BARA LIME



Barium hydroxide and calcium hydroxide are moulded and compressed into pellets. The barium hydroxide is more active and soluble than the calcium and serves as the activator. One pound lasts six to eight hours intermittent use.

**APPARATUS**—Two types—to and fro and circle type inhalers are currently used. Both are satisfactory. They possess the following features, advantages and disadvantages.

## ADVANTAGES OF CARBON DIOXIDE ABSORPTION

1. Allows inhalation of warmed gases and vapors—conserves heat.
2. Allows little or no fluctuation in depth of anesthesia.
3. Excludes flammable mixtures.
4. Allows use of high oxygen tensions.
5. Allows use of positive pressure.
6. Economical.
7. Mitigates against water loss through lungs.

## DISADVANTAGES OF CARBON DIOXIDE ABSORPTION

1. Increases complexity of apparatus for administration of inhalation anesthesia.
2. Possibility of inhaling alkaline dust.
3. Absorbent—may act as a catalyst and decompose agents—may favor explosion.
4. Excessive heat may be generated by chemical reaction.

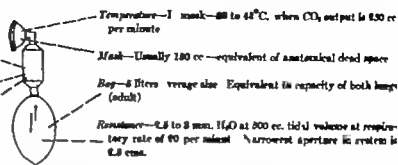
**TO AND FRO**—Consists of a mask attached to a cylindrical canister and breathing bag. During expiration gases pass from mask to canister to bag; during inspiration direction is reversed. A closely fitting mask allows complete rebreathing of all gases. Metabolic oxygen requirement must be added.

#### FEATURES

**Canister**—Must accommodate tidal volume of patient in the inter- and intragranular spaces for efficient absorption.

**Size**—8×13 cm. Accommodates 800 gm. of 8 mesh soda lime. Has an intergranular and intragranular air space of 483 cc.

**Material**—Metal preferred for stability and to help dissipate heat.



#### Advantages of To and Fro Filter

- (1) Apparatus close to head and accessible for controlled breathing.
- (2) Gases pass over absorbent tissue yielding more efficient absorption.
- (3) Inspired air is warm.
- (4) Minimal resistance to valves or long tubing.
- (5) Apparatus simple. Absence of mechanical parts which may become damaged.

#### Disadvantages of To and Fro Filter

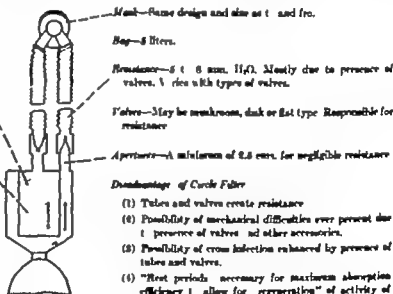
- (1) Proximity to face favors inhalation of alkaline dust.
- (2) Proximity to face may cause excessively hot gases to be inhaled.
- (3) Dead space from lips to mask becomes progressively greater as absorbent is exhausted.
- (4) Efficiency reduced if air space in canister does not equal tidal volume.
- (5) Difficult to approximate and hold on face.

**CIRCLE FILTER**—An inhaler composed of a mask, bag and canister. A valve at the inlet and outlet of the canister permits only a unidirectional flow of gases. Two corrugated tubes approximately 30" long connect the mask to the canister.

#### FEATURES

**Canister**—Inter- and intragranular air space must equal or be greater than tidal volume of patient for optimum efficiency. May be greater but efficiency falls if air space is less than tidal volume.

**Temperature**—Tissue usually 39 to 41°C. in mask at 630 cc. CO<sub>2</sub> output per minute at 42°C. (45 to 48°C. in canister).



#### Advantages of Circle Filter

- (1) Inspired gases cooler than in to and fro (39 to 41°C.).
- (2) Possibility of inhaling dust minimized by long tubing.
- (3) Easier to manipulate—canister is placed away from face.
- (4) Absorption equally as efficient as to and fro.
- (5) Less "dead space" in tubes from mask to filter than in to and fro.

#### Disadvantages of Circle Filter

- (1) Tubes and valves create resistance.
- (2) Possibility of mechanical difficulties over present due to presence of valves and other accessories.
- (3) Possibility of cross infection enhanced by presence of tubes and valves.
- (4) "Rest periods" necessary for maximum absorption efficiency to allow for "regeneration" of activity of soda lime.

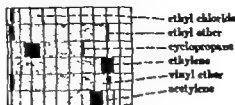
**REGENERATION OF ACTIVITY**—Sodium carbonate and calcium carbonate form when carbonic acid neutralizes the hydroxides, the former preferentially. Sodium carbonate is soluble; calcium carbonate totally insoluble. Interaction of soluble sodium carbonate with unused calcium hydroxide still present in partially exhausted granule yields insoluble calcium carbonate and regenerates sodium hydroxide which reactivates the absorbent.



## FIRES AND EXPLOSIONS

## PREDISPOSING FACTORS

1. **Inflammable Materials**—Most anesthetic drugs burn readily. They contain C, H and O. Halogens tend to decrease inflammability. Concentrations of agents required for anesthesia (black areas) fall within explosive limits (shaded areas).



2. **Oxygen Supply**—Limits of oxygen concentration required for combustion with anesthetic agent (black) less than physiological requirements (shaded). The more intimate the mixture the more rapid the combustion and usually the more destructive the response.



Ether is heavier than water. Only one layer of molecules can combine with oxygen.



Equal amount of ether vaporized explodes. All molecules combine with oxygen at same time. Steam and expanding  $\text{CO}_2$  form.

3. **Ignition Source**—Ignition temperature varies with mixture and material. Some mixtures require longer period of contact with ignition temperature to self-sustain combustion than others. The higher the flash point, the safer the compound. In anesthesia, the ignition source may be inadvertently provided by:

Flames	Electricity	Static Electricity	Miscellaneous
Pipes	Motors	Friction from motions of people	Spontaneous combustion
Cigarettes	Heaters	gases	Oil on oxygen or air valves
Gas and	X-rays	parts of equipment	under pressure
Alcohol lamps	Cauterizers	blankets	
	Poor switches	bags	
	Endoscopes	tables	
	High frequency units	adhesive removal	

4. **Miscellaneous Factors**—Size and shape of containers and pressures of vapors or gases cause inflammability to vary. Propagation in horizontal direction greater than vertical. Dilution with inert gases ( $\text{CO}_2$ ,  $\text{N}_2$ ,  $\text{He}$  etc.) lowers limits of inflammability because these gases possess a high heat capacity or high rate of heat conduction.

## PREVENTIVE PROCEDURES

1. Provide closed system—high humidity (65% discharges static).
2. Provide adequate ventilation to dilute and diffuse vapors.
3. Wash apparatus with inert gas after each use. Rinse with water.
4. Use pure agents—ether peroxides have low ignition temperatures.
5. Avoid sudden movements of personnel, clacking of metals, and friction.
6. Use spark proof electrical equipment. Avoid cautery and high frequency circuits.
7. Provide intercoupling—interconnecting apparatus, operator and patient with high resistance (of 1 megohm) allows slow discharge of highly charged body and prevents sparks.
8. Provide conductive rubber.
9. Eliminate sources of static electricity—woolen blankets, nylon and silk clothes, rubber soled shoes.



# GLOSSARY

Absolute zero	(0°A.) 273° below 0°C. At this temperature molecular motion is believed to cease
Absorption	Passage of a substance into the interior of another by solution or penetration.
Acapnia	Decrease of carbon dioxide tension in blood below that required to maintain stimulation of the respiratory center
Acetabula	Reduction of blood carbonates and bicarbonates below normal.
Acid	A substance which yields hydrogen ions (H <sup>+</sup> ) in solution. Really a substance which yields osmium (H <sub>2</sub> O <sup>+</sup> ) in aqueous solution.
Acid anhydride	A non-metal oxide which reacts with water to form an acid.
Acid salt.	A salt containing one or more replaceable hydrogen atoms (NaHCO <sub>3</sub> )
Action potential	Current produced during physiological activity of nerve or other tissue
Activate	To induce a state of increased chemical activity
Activated charcoal	Charcoal treated to increase its absorptive power
Acyclic	An open chain compound possessing ring formation.
Acyl group	An organic radical having the configuration $R-\overset{\overset{O}{\parallel}}{C}-$
Additive effect.	Effect caused by simultaneous administration of two similar drugs represented by arithmetical average
Addiction	Physical dependence to a drug resulting in the abstinence syndrome upon withdrawal. Organic symptoms and mental fixations follow
Adsorption	A process believed to be physical in nature in which molecules of a gas or liquid condense or adhere as film, on the surface of another substance.
Agent (anesthetic)	Term used by anesthesiologists to designate an anesthetic drug.
Alveary	Pathway for inspired air from lips and nostrils to alveoli.
Alcohol	An organic compound, derived from hydrocarbon, containing one or more hydroxyl (OH) groups.
Aldehyde	An organic compound, derived from hydrocarbon, containing $\overset{\overset{O}{\parallel}}{C}-H$ group
Aliphatic	Open-chain, organic compounds.
Alkal	A strong, water soluble base
Alkaloid	Physiologically active substance derived from plants, usually having a complex chemical structure containing nitrogen, and possessing basic properties. (Names usually end with "ine")
Alkyl	Radical derived from an aliphatic hydrocarbon, produced by removing one hydrogen from it. A radical cannot exist alone as such (—CH <sub>3</sub> methyl)
Allotropy	The ability of certain elements to exist in more than one form, due to a particular arrangement of the atoms or molecules.
Amalgam	An alloy composed of mercury and one or more metals. The metal dissolves in the mercury
Amaroid	A bitter principle obtained from plants.
Amide	Amino acids whose hydrogen replaced by an acyl group $R-\overset{\overset{O}{\parallel}}{C}-NH_2$
Amine	Substance produced by replacing one or more hydrogen atoms of ammonia by alkyl or aramatic, aliphatic or heterocyclic radicals. R—NH <sub>2</sub> —primary; R <sub>2</sub> NH—secondary; R <sub>3</sub> N—tertiary
Amorphous	A substance which does not have or does not appear to have crystalline structure
Amphoteric substance	A substance which possesses radicals which exhibit both acidic and basic properties COOH—R—NH <sub>2</sub> .
Anesthetic index	No. units of anesthetic required for anesthesia
	No. units of anesthetic required for respiratory failure
Anesthetic salt	10 <sup>-3</sup> cm., a hundred millionth of a centimeter
Anhydride	The residue after the elements of water are abstracted from an acid or base
Anhydrous substance	A substance free from water
Anion	A negatively charged ion which is attracted to the anode (electrode where oxidation occurs) Cl <sup>-</sup> Br <sup>-</sup> CO <sub>3</sub>
Antagonism	Opposing action of one drug by another (negative anesthesia)
Aromatic	Group of compounds derived from benzene and related hydrocarbons.
Association	The union of acyclic similar molecules to form complex molecules. Such a union is reversible and remains incomplete X(H <sub>2</sub> O) → (H <sub>2</sub> O) <sub>n</sub>
Atom	The smallest unit of an element which takes part in the formation of a compound. An atom is a positive nucleus surrounded by electrons
Atomic number	The net positive charge on the nucleus. This represents the number assigned to the atom in the periodic table
Atomic weight	The weight of an atom compared to the weight of an oxygen atom taken as 16.000.
A-V difference	Difference in volumes per cent between content O <sub>2</sub> of arterial and venous blood.
Avogadro's hypothesis	Hypothesis stating that at the same temperature and pressure equal volumes of gases contain the same number of molecules.
Avogadro's number	The number of molecules in gram-molecule (mole) 6.06X10 <sup>23</sup>

<b>Base</b>	(1) A hydronide of a metal which yields hydroxyl ions in solution and neutralizes an acid to form a salt and water (2) A substance capable of combining with a proton.
<b>Basic anhydride</b>	The oxide of a metal which forms a base when it reacts with water.
<b>Basic salt</b>	A salt containing replaceable or hydroxyl groups.
<b>Binary compound</b>	A compound whose molecule is composed of two elements.
<b>Boiling point</b>	The temperature at which the vapor pressure within a liquid equals atmospheric pressure.
<b>Brownian movement</b>	The random agitation of particles of molecular magnitude produced by collision of molecules.
<b>Calorie</b>	The amount of heat required to raise the temperature of one gram of water from 14°C. to 15°C. The large calorie which is used in nutrition equals 1000 calories.
<b>Calorimeter</b>	An apparatus used to measure the amount of heat liberated or absorbed during a chemical or physical reaction.
<b>Carbonyl</b>	C=O group, characteristic of ketones but also present in other radicals.
<b>Carboxyl</b>	—C(=O)—OH group, characteristic of organic acids.
<b>Catalysis</b>	The change in the rate of a chemical reaction induced by the presence of a substance (called catalyst) which is itself unchanged after the reaction is completed.
<b>Cathode</b>	(1) The negative electrode of an electrolytic cell. (2) The electrode where reduction occurs.
<b>Cation</b>	A positively charged ion which migrates to the cathode in electrolysis.
<b>Chemical equilibrium</b>	The state of balance between two chemical reactions proceeding at equal rates but in opposite direction, each undoing the work of the other.
<b>Complex ion</b>	Ions produced by the union of a number of simple ions, or by the union of a simple ion with molecules.
<b>Complex salt</b>	A salt which contains complex ions.
<b>Compound substance</b>	A substance which can be decomposed into recognized elements.
<b>Conjugation</b>	Addition of a new group by a biochemical mechanism to a chemical substance which changes its physiological activity (glycine and benzoic acid—hippuric acid)
<b>Covalent molecule</b>	A molecule in which the bond between two atoms is a shared electron pair such as H <sub>2</sub> , Cl <sub>2</sub> , H <sub>2</sub> O, CH <sub>4</sub> .
<b>"Cracking"</b>	A process in which hydrocarbons of high molecular weight are broken down into smaller molecules by the aid of heat and pressure.
<b>Critical pressure</b>	The minimum pressure required to liquefy a gas at the critical temperature.
<b>Critical temperature</b>	The temperature above which a gas cannot be liquefied regardless of the pressure used.
<b>Crystalloid</b>	A material which when dispersed in a dispersion medium forms a true solution.
<b>Cyclic</b>	Closed-chain chemical compound (cyclopropane)
<b>Degradation</b>	A disintegration of a chain of carbon atoms in a stepwise manner.
<b>Density</b>	Mass per unit volume, e.g., grams per cubic centimeter.
<b>Depression</b>	Decrease of power of cells to function.
<b>Derivative</b>	The resultant of a chemical reaction.
<b>Detonator</b>	Flame, fuse, shock or other agent which causes an explosive mixture to explode.
<b>Dextrorotatory</b>	Rotating a plane of polarized light to the right.
<b>Dibasic acid</b>	Acid with two replaceable hydrogen atoms in its molecule.
<b>Diffusion</b>	(1) Passage of molecules through membranes (such as in dialysis); (2) The spreading apart of molecules of gases or fluids.
<b>Distillate</b>	The vapor which condenses and is caught in the receiver of a distillation apparatus.
<b>Dissociation</b>	Reversible decomposition of complex molecules into simpler molecules.
<b>Dissolve</b>	The dispersion of one material into another so that an apparently homogeneous mixture forms. There may or may not be chemical alterations.
<b>Dose</b>	Toxic—Amount of drug which causes untoward symptoms in the average individual (also fatal dose) Minimum Lethal (M.L.D. 50) The amount of drug fatal to 50% of the animals in controlled experimental conditions. Minimal—Smallest amount of a drug which has therapeutic effects. Maximal—Largest amount of drug which can be tolerated without toxic symptoms. Therapeutic—Dose lying somewhere between minimal and maximal.
<b>Double salt</b>	A salt in which two atoms of a metal are combined with one acid radical or one atom of a metal is combined with two acids.
<b>Drug</b>	A chemical agent which affects living protoplasm.
<b>Dyne</b>	The force necessary to impart to a mass of one gram an acceleration of one centimeter per second per second.
<b>Effervescent substance</b>	A substance which loses water of crystallization when exposed to air e.g., Na <sub>2</sub> CO <sub>3</sub> ·10H <sub>2</sub> O → Na <sub>2</sub> CO <sub>3</sub> ·H <sub>2</sub> O + 9H <sub>2</sub> O
<b>Electron</b>	The unit of negative electricity which possesses a mass equivalent to 1/1815 of the hydrogen atom.
<b>Elementary substance</b>	One of a small group of substances of nearly complete stability whose chemical properties give each of them a definite place in the Periodic Table.
<b>Emulsion</b>	A dispersion in which the dispersed phase is a liquid and dispersion medium is a liquid.
<b>Endotherm</b>	Arising from sources within the organism.
<b>Endothermic</b>	Reaction absorbing heat.
<b>End point</b>	The completion of a reaction usually evident by the first perceptible alteration of the color of an added indicator.

<b>Enzyme</b>	A substance liberated by living cells which possess catalytic properties.
<b>Epoxy</b>	A group which has the structure $\begin{array}{c} \text{O} \\   \\ -\text{C}-\text{C}- \\   \quad   \end{array}$
<b>Equilibrium</b>	A state of balance between opposing forces or processes.
<b>Exogenous</b>	Arising from without the organism or system.
<b>Exothermic</b>	Reaction accompanied by the evolution of heat.
<b>Explosive mixture</b>	Mixture capable of extremely rapid or almost instantaneous combustion, the expansive force of which is destructive.
<b>Extract</b>	Concentrated preparation of animal or vegetable drug obtained by solution from source and concentrating preparation to prescribed standard.
<b>Fermentation</b>	A chemical reaction accomplished by living cells & liberates energy anaerobically aided by enzymes.
<b>Flash point</b>	Lowest temperature at which vapors of a liquid may be ignited by a flame.
<b>Fluid extract</b>	Liquid preparation of vegetable drug containing alcohol as solvent or preservative. Each cc. contains therapeutic equivalent of 1 gm. standard drug it represents.
<b>Fluorescence</b>	A process in which light is absorbed and is instantaneously re-emitted with altered frequency.
<b>Foam</b>	A dispersion in which the dispersed phase is gas and the dispersion medium is a liquid.
<b>Fractional distillation</b>	The process by which two or more liquids of different boiling points are separated by distillation and each fraction, as it forms, is collected in separate containers.
<b>Glycoside</b>	Neutral principle containing a carbohydrate molecule in conjunction with one or more chemical bodies.
<b>Gram atom</b>	Atomic weight of an element expressed in grams.
<b>Gram molecule</b>	The molecular weight of an element or compound expressed in grams.
<b>Habitation</b>	A condition characterized by "psychic craving" which follows continued use of drug.
<b>Halide</b>	A substance composed of a radical and one or more halogen atoms.
<b>Halogens</b>	The elements fluorine, chlorine, bromine, and iodine.
<b>Heat of dissociation</b>	The heat (expressed in calories) expended in the dissociation of one mole of a substance into specified products.
<b>Heat of formation</b>	The heat in calories which is absorbed or liberated during the reaction in which a mole of compound forms from the necessary elements.
<b>Heat of vaporization</b>	Heat in calories required to change a unit weight of liquid to the vapor state at a given temperature.
<b>Heterocyclic</b>	Cyclic structures containing other elements beside carbon in the ring.
<b>Humidity (absolute)</b>	The amount of a dry vapor present per unit volume of gas or air when saturated at given temperature.
<b>Humidity (relative)</b>	The actual amount of water vapor present in the air or a gas divided by the amount necessary for saturation at the same temperature and pressure expressed in per cent.
<b>Hydrogenation</b>	Process of adding hydrogen (i. e. an unsaturated compound).
<b>Hydrate</b>	A crystalline substance containing a definite proportion of chemically combined water.
<b>Hydrolysis</b>	Reaction between the ions of salt and those of water forms an acid and base one or both of which is only slightly dissociated.
<b>Hydrus</b>	Combined with an indistinct or variable amount of water.
<b>Hygroscopic</b>	A substance which absorbs moisture from the atmosphere.
<b>Hyperbaric</b>	Specific gravity of a solution which is greater than that of spinal fluid.
<b>Hypobaric</b>	Specific gravity of a solution less than that of spinal fluid.
<b>Ictidysarcia</b>	Abnormal or unusual response to drug even to extremely small doses.
<b>Indicator</b>	A substance capable of undergoing a color change to definite hydrogen ion (or other specific ion) concentration.
<b>Induction</b>	Period from start of anesthetic attainment of third stage.
<b>Inert element</b>	An element located in the zero group of the Periodic Table.
<b>Interface phase</b>	The surface which separates two phases of a mixture.
<b>Ion</b>	A atom or group of atoms bearing positive or negative charge.
<b>Ionization</b>	The formation of ions by interaction of a substance with solvent.
<b>Isoelectric point</b>	The pH at which an amphoteric colloid exhibits minimum of swelling and may be nearly precipitated.
<b>Iso</b>	A prefix placed before the name of an aliphatic compound indicating branching of the chain.
<b>Isobaric</b>	A solution having the same specific gravity as spinal fluid.
<b>Isomerism</b>	Substances which have the same composition but different molecular structures.
<b>Isomers</b>	Molecules composed of the same number and types of atoms but which are arranged differently within the molecule.
<b>Isotopes</b>	Atoms which possess the same atomic number but slightly different atomic weights due to differences in number of particles in the nuclei. Usually possess almost identical chemical properties.
<b>Latent heat</b>	The quantity of heat expressed in calories which is absorbed or liberated when a mole of substance changes from one state to another at fixed temperature. e. g. conversion of 18 g. of ice to water at 0°C. requires 1440 calories of heat or 80 calories per gram.

<b>Latent heat of vaporization</b>	The amount of heat in calories required to change unit mass of a substance existing in a liquid form at a given temperature into a vapor without change of temperature. The heat of vaporization for water at 100°C. is approximately 539 calories per gram.
<b>Law Le Chatelier's</b>	If external factors such as temperature and pressure disturb a system in equilibrium adjustment occurs in such a way that the effect of the disturbing factors is reduced to a minimum.
<b>Leverotatory</b>	Rotating the plane of polarized light to left.
<b>Lipophile</b>	Showing marked attraction or solubility in lipoids.
<b>Macerate</b>	The process of softening a solid by steeping it in a liquid.
<b>Margin of safety</b>	Margin between the therapeutic dose and lethal dose.
<b>Melting or freezing point.</b>	The temperature at which the solid and liquid phases of any pure substance are in equilibrium.
<b>Mercaptan</b>	An alcohol in which sulphur replaces oxygen in the hydroxyl group to form an (SH) group.
<b>Misomer</b>	A chemical compound which resembles another in properties but differs from it in structure and composition.
<b>Molal</b>	A solution in which one gram-molecular weight of solute is dissolved in one thousand grams of solvent.
<b>Molar solution</b>	A solution which contains one mole of solute per liter of solution.
<b>Mole</b>	The molecular weight of a substance expressed in grams.
<b>Molecular weight</b>	The sum of the atomic weights of all the atoms in a molecule.
<b>Monobasic acid.</b>	An acid having one replaceable hydrogen atom in its molecule.
<b>N</b>	Refers to Nitrogen—A radical is attached to nitrogen in a compound. N-methyl means a methyl group attached to the nitrogen atom.
<b>n</b>	Normal—Refers to straight-chain compound n-propane.
<b>Nascent</b>	The state of an element at the instant it is liberated from a compound.
<b>Neutral principle</b>	Drugs obtained from plant or animal sources which are neutral in reaction (names end with "in")
<b>Neutralization</b>	Union of hydrogen and hydroxyl ions to form undissociated molecules of water.
<b>Neutral solution</b>	A solution containing an active reagent which may replace with, liberate, or cause to react with one gram of hydrogen per liter.
<b>Oxidation</b>	The process by which large volumes of gases are absorbed by solids.
<b>Oxidation</b>	(1) The combination of oxygen with other elements to form oxides. (2) The process in which an element gains electrons.
<b>Oxidation potential</b>	The measure of the tendency of a substance to be oxidized to some specified other substance, under specified conditions.
<b>Oxonium ion</b>	The ion $\text{H}_2\text{O}^+$ formed by direct union of a proton with water. The oxonium ion forms when an acid dissolves in water. The acid moment was that hydrogen ( $\text{H}^+$ ) ion was formed.
<b>Oxygen capacity (vol. %)</b>	Maximum amount of oxygen a given volume of blood absorbs when equilibrated with an excess of oxygen expressed in cc. per 100 cc.
<b>Oxygen content (vol. %)</b>	Oxygen in volumes per cent present in blood at a given moment.
<b>Oxygen saturation</b>	Oxygen content divided by oxygen capacity expressed in volumes per cent.
<b>Perilysis</b>	Cessation of cell function.
<b>Periodic table</b>	A table of the elements, arranged in rows and columns. The different columns represent different groups of chemically similar elements.
<b>pH</b>	Concentration of hydrogen ions expressed as the logarithm of the reciprocal of the concentration.
<b>Pharmacodynamics</b>	The study of the action of drugs on the living organism.
<b>Pharmacotherapeutics</b>	Study of drugs and use in relation to treatment of disease.
<b>Pharmacology</b>	Study of physical characteristics of crude drugs.
<b>Pharmacy</b>	Art of preparing, compounding, and dispensing drugs and medicines.
<b>Phase</b>	A homogeneous portion of matter which is distinct in composition and properties from other phases in contact with it.
<b>Phase</b>	Level or "stratum" of third stage anaesthesia.
<b>Polymer</b>	A new compound formed by the combination of several molecules of a substance. The compound has a percentage composition the same as the initial compounds but the molecular weight is a multiple of the initial compound.
<b>Polysorption</b>	The ability of a substance to exist in two or more crystalline forms.
<b>Potentiation</b>	Addition of one drug, not necessarily possessing similar action, to another to increase its action.
<b>Precipitate</b>	An insoluble solid substance which forms from chemical reactions between solutions.
<b>Pressure</b>	The force exerted against a unit area usually expressed in dynes or grams per square centimeter or in pounds per square inch.
<b>Proton</b>	A positively charged hydrogen atom, $\text{H}^+$ which is identical with the hydrogen nucleus.
<b>Qualitative test</b>	A test which attempts to identify a material or the ingredients of a mixture.
<b>Quantitative test</b>	A test used to determine the actual amount of a given substance in a mixture or compound.
<b>Racemic</b>	A mixture of equal portions of a dextro and a levo compound. There is no rotation of the plane of polarized light.
<b>Radical</b>	A group of atoms capable of acting as single elements in chemical reactions ( $\text{CO}_3$ ; $\text{BO}_3$ ; $\text{PO}_4$ ; etc.)

<b>Radioactive</b>	Refers to a substance capable of a continuous discharge of invisible rays, which affect the photographic plate, the electroscope, or produce a visible fog in moist air.
<b>Reactivity</b>	Possessing the tendency toward entering into a specified chemical reaction.
<b>Rectify</b>	Purification of a substance by fractional distillation.
<b>Reduction</b>	Removal of oxygen; addition of hydrogen; gain of electrons.
<b>Reducing agent</b>	(1) A substance capable of removing oxygen from another substance. (2) A substance which contains an atom which donates one or more electrons.
<b>Replacement series</b>	An arrangement in which the metals are listed in order of their decreasing chemical activity.
<b>Reversible reaction</b>	A reaction which under proper conditions can proceed in both directions at one time.
<b>Saponification</b>	The hydrolysis of fats and oils by alkalis and water to form soaps and alcohols.
<b>Saturated solution</b>	A solution in which an equilibrium exists between undissolved solute and dissolved solute.
<b>Saturated vapor</b>	This condition is present when the space above a liquid contains all the vapor it can acquire and hold at the given temperature and which is in equilibrium with the liquid.
<b>Soluble</b>	The substance which dissolves in a solvent.
<b>Solvent</b>	The constituent of a solution which does the dissolving and is present in greater amounts than the solute.
<b>Specific gravity (gases)</b>	The ratio of the weight of one liter of gas compared to the weight of one liter of air.
<b>Specific gravity (solid or liquid)</b>	The ratio of the weight of a unit volume of a substance to the weight of an equivalent volume of water.
<b>Specific heat</b>	The heat required to raise the temperature of one gram of a substance from 14-15°C.
<b>Spectrum</b>	The separation of light into its component parts by the aid of a prism or grating.
<b>Stable</b>	A term applied to a substance which has no tendency to decompose spontaneously.
<b>Stability (as applied to compounds)</b>	The property of being able to resist being decomposed or chemically altered.
<b>Standard conditions</b>	0°C. and 1 atmosphere pressure (760 mm. Hg).
<b>Standard atmospheric pressure</b>	The pressure caused by the weight of the atmosphere at sea-level. It is a pressure of 1033 grams per square centimeter or 14.7 pounds per square inch. It elevates mercury in a barometer to a height of 760 mm.
<b>Stimulation</b>	Increased functioning of protoplasm induced by some extracellular substance or agent.
<b>Strong acid</b>	An acid which is completely ionized in aqueous solution.
<b>Sublimation</b>	The transformation of a solid to a vapor without its passing through the liquid state.
<b>Supercooling</b>	The cooling of a liquid below its freezing point, without freezing occurring.
<b>Summation</b>	The combined action of two drugs given simultaneously equal the algebraic sum of their individual effects.
<b>Surface tension</b>	Contraction force of a surface, usually expressed in dynes per square centimeter.
<b>Suspension</b>	A dispersion in which the dispersed phase is composed of a solid.
<b>Synergism</b>	Spontaneous shrinkage of a gel, accompanied by slow separation of liquid.
<b>Synergism</b>	Production of an effect by two drugs possessing similar action acting together which is greater than the sum of each if they act alone (positive summation).
<b>Tension</b>	Pressure of a gas.
<b>Tertiary compound</b>	A compound whose molecule is composed of three elements.
<b>Thio</b>	Prefix indicating sulphur-containing compound.
<b>Tincture</b>	Alcoholic solution of a drug. Usually contains 10 grams of crude drug per 100 cc. of solution.
<b>Titration</b>	The measurement of the volume of liquid needed to complete a given chemical reaction.
<b>Tolerance</b>	The need to progressively increase a dose of a drug to maintain a given therapeutic response with repeated administration.
	Cross tolerance—Resistance to action of given drug results in tolerance to a chemically related drug possessing similar actions.
	Individual—Tolerance to a drug which a subject has never received before.
	Species—Inactivity species exhibits to particular drug.
<b>Trifluoric acid</b>	An acid containing three replaceable hydrogen atoms in each molecule.
<b>Valence</b>	(1) The number of atoms of hydrogen (or equivalent elements) which combine with, or are replaced by the atom in question. (2) Polar valence is the excess of positive or negative charges on an atom or radical. (3) Non-polar valence is the number referring to electron pairs shared with other atoms.
<b>Vapor density</b>	The ratio of the weight of gas or vapor to the weight of an equal volume of hydrogen measured under the same conditions of temperature and pressure.
<b>Vapor pressure</b>	The partial pressure exerted by a vapor.
<b>Viscosity</b>	Resistance to flow of fluids due to the internal friction of the liquid.
<b>Volutes per cent</b>	(Blood) or of gas liberated from 100 cc. of liquid.
<b>Water of hydration</b>	The water contained in a hydrate.
<b>Weak acid</b>	An acid which is only slightly ionized in aqueous solution.

## ATOMIC WEIGHTS

<i>Element</i>	<i>Symbol</i>	<i>Exact Weight</i>	<i>Approximate Weight</i>
Argon	A	18	18
Barium	Ba	137.36	137
Bromine	Br	79.918	80
Calcium	Ca	40.08	40
Carbon	C	12.01	12
Chlorine	Cl	35.45	35
Copper	Cu	63.57	63
Fluorine	F	19.00	19
Helium	He	4.003	4
Hydrogen	H	1.008	1
Iodine	I	126.94	127
Iron	Fe	55.84	56
Lithium	Li	6.94	7
Mercury	Hg	200.61	201
Neon	Ne	20.18	20
Nitrogen	N	14.008	14
Oxygen	O	16.00	16
Phosphorus	P	31.00	31
Potassium	K	39.00	39
Sodium	Na	22.997	23
Sulphur	S	32.06	32
Zinc	Zn	65.38	65

## CONVERSION FACTORS FOR METRIC SYSTEM

	<i>Exact</i>	<i>Approximate</i>
1 cubic centimeter	10 cc mililiter	15 minims
1 liter (1000 cc)	23 8 fl. oz.	1 qt.
1 milligram	0.0154 grain	1/60 gr.
1 gram	15.432 grains	15 gr.
1 grain	64.8 milligrams	64 mgm.
1 drachm	3.88 grams	4 gm. or 4 cc.
1 ounce	28.35 grams	50 gm. or 50 cc.
1 millimeter	—	1/25 inch
1 inch	2.54 cm.	2.5 cm.
1 pint (16 oz.)	473.00 cc	500 cc

## TEMPERATURE CONVERSION FACTORS

Fahrenheit to Centigrade—Subtract 32 from F. reading and multiply by 5/9  
 Centigrade to Fahrenheit—Multiply C. by 9/5 and add 32 to the result.



<i>Drug</i>	<i>I filtration</i>	<i>Intrarectal</i>
<b>Local anesthetic</b>		
allylamine hydrochloride	.5-4%	
apotheline hydrochloride	.5-4%	2 cc. of a 4% solution
carbazone hydrochloride	6%	
larocaine hydrochloride	2.5-4%	
metyscaine hydrochloride	.5-1%	
suxamethane hydrochloride	1/1000 solution up to 100 cc	15-40 cc. of 1/1000 solution in .5% saline (Jones)
pentocaine hydrochloride		15-40 mgm.
procaine hydrochloride	.5-1%	100-180 mgm.

## QUALITATIVE TESTS

**Peroxides in ether**

Potassium iodide (10%) 3 cc.

Ether 5 cc.

Shake stopper, keep in dark place 40-60 minutes. Yellow color in ether layer indicates presence of peroxides—sensitive to .0005% peroxide

**Aldehydes in ether**

Nessler' solution 3 cc.

Ether 20 cc.

Immediate yellow color or precipitate indicates presence of aldehydes. Test positive if mixture stands, due to oxidation of alcohol | the ether

**Bertholates in urine**

Extract urine (acidified) with 10 volumes of chloroform per unit volume.

Chloroform extract 1 cc.

Isopropyl acetate 8% in absolute methyl alcohol 0.6 cc.

Cobaltous acetate (1%) in absolute methyl alcohol 0.1 cc.

Reddish violet color indicates positive reaction.



1

Adrian  
Adrian and Rovenstine  
Adrian and Rovenstine  
Barbour  
Barlow  
Barber and Bourne  
Barroff and Rothchild  
Bartido  
Beecher  
Bischof  
Blair  
Bolliger  
Bolton  
Bousyoskie  
Bourne  
Bourne and Strick  
Bord  
Bord  
Bord  
Borkman and Wardell  
Boslow  
Borge  
Borge, Wickwire et al.  
Campbell and Morgan  
Case and Giers  
Chamberlain  
Carmore and Schmidt  
Corylin and Baralana  
Crosby, Grossman and Blauwhite  
Cullen  
Dallmann  
Dallman, et al.  
Derkschle et al.  
Dooley and Wille  
Fader  
Faverson  
Ernst  
Farson, Carr and Krieger  
Fawcett and Collins  
Frickman and Reed  
Freyberg  
Gonzalez, Vasez and Halpern  
Gardel  
Gardel  
Gardner  
Guthrie  
Hase  
Henderson  
Henderson and Haggard  
Hewer  
Hoff  
Hoppers  
Howard, Blumrich and Adams  
Imberger  
Jewell and Farquar  
Jones  
Kawell  
Kurtz, Bennett and Shapiro  
Larson, Smith, et al.  
Leigh  
Lorenson

- 100

- Lucas  
MacNider  
McDonald  
May  
Merk  
Merk, Nathanson and Orth  
Mergle  
Miller  
Molera Hospital  
Murphy and Young  
Mushin  
Ney  
Pharmacopoeia of U.S.  
Quastel and Wheatley  
Rabinowitch  
Rabinowitch  
Racker  
Ryden  
Severin, DePaolo and Evans  
Severin  
Severin and Weiss  
Severin and Rose  
Severin and Van Lier  
Smith  
Solomon  
Taylor and Waters  
Tha  
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Crawford  
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Davies  
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Bryant  
Dripps  
F. y. Anderson and Keyes  
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Henderson and Lucas  
Henderson and Lucas  
J. A. M. A.  
Knaiz  
Murphy, Crumpton & Mink  
Neff and Mink  
Orth and Mink  
Ragunsky and Bourne  
Roberts  
Roberts and Baxter  
Roberts and Baxter  
Rosenberger  
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 Black  
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 Eastman  
 Eascom  
 Evans and Krantz  
 Farber, McIntosh and Sefton  
 Forbes and Miller  
 Forbes and Miller  
 Forbes and Miller  
 Fujii  
 Geraciotti and Marvizi  
 Ghose  
 Gold and Sussman  
 Gudel and Treweek  
 Higard  
 Hines and Milliken  
 Hark  
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 Krantz, Jelliffe, et al.  
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 McMeister and Rast  
 Mowbray and Topley  
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 Fisher and Soliman  
 Pringle, et al.  
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Miller  
Orrett and Severs  
Orrett and Waters  
Severs and Waters  
Weight and Thompson

## HYDROCARBONS

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Henderson and McDonald  
Kraatz, Carr et al.  
Kraatz, Carr and Vitche  
Severs and Waters  
Stoughton  
Vitke

## ETHYLENE

Bouchart  
Johnson and Ivy  
Leske and Hertman  
Lushardt and Carter  
Lushardt and Carter  
Miller and Plant  
Newman  
Nikolov and Ivanovitch  
Sherris, Swadlow and McElroy

## CYCLOPROPANE

Adriani  
Adriani and Rosenzweig  
Allen, Stetson, et al.  
Allen, Stetson and Meek  
Allen, Stetson and Meek  
Bourne  
Bartlett  
Bartlett  
Dripps  
Fay, Anderson and Keryon  
Gardel  
Hale, McEer, Hinde and Giesenbrunsp  
Henderson and Lucas  
Henderson and Lucas  
J.A.M.A.  
Knight  
Murphy, Crumpton & Meek  
Nell and Stiles  
Orth and Meek  
Raginsky and Bourne  
Robbins  
Robbins and Baxter  
Robbins and Baxter  
Rosenberger  
Schackel and Eisenmuth  
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Bourne  
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Cattell  
Dale and Haddfield  
Eastman  
Emerson  
Evans and Krantz  
Forbes, McIntosh and Sefton  
Foster and Miller  
Forbes and Miller  
Forbes and Miller  
Fuji  
Gerschlager and Marcus  
Gibbs  
Gold and Rosenman  
Gordal and Treweek  
Haggard  
Haines and Middleton  
Hark  
Kerten and Ross  
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Krantz, Evans, et al.  
Krantz, Jeffrey, et al.  
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Jackson  
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Gardner and Leach  
Harnack and Meyer  
J.A.M.A.  
Maciz  
Parsons  
Pitt  
Ragnaky and Bourne  
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## THE PHARMACOLOGY OF ANESTHETIC DRUGS

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Adrian  
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Barlow  
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Beyer and Latron  
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Burnstein  
Burstin and Revenstine  
Burtzfeld  
Dille  
Dille  
Duel and Chambers  
Ellis and Barlow  
Emge and Hoffman  
Evans, et al.  
Everett and Richards  
Finerger and Cobb  
Fitch and Tatum  
Fulton and Jellies  
Goumar, Cordill, et al.  
Gower Tatum, et al.  
Green and Koppányi  
Gruber  
Gruber and Babbett  
Gruber and Freedman  
Gruber, Hany and Gruber  
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Horsley  
Irving, Bertram and Nelson  
Johnston  
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Nowak  
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Omsted and Giragomits  
Pratt  
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Roth  
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Everett  
Hardy Wolff & Goodell  
Lee  
Lehman  
New and Non-official Remedies  
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Adrian  
Barbier and Tavel

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## BARBITURATES

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Adrian  
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Argy Langer, Dille  
Barlow  
Beecher and McCarroll  
Beyer and Laitva  
Bozros, Baginsky  
Burdick and Rowanstone  
Burnstein  
Burnstein and Rowanstone  
Buttural  
Dille  
Dille  
Doel and Chambers  
Ellis and Barlow  
Enage and Hoffman  
Evans, et al.  
Everett and Richards  
Flannery and Cobb  
Fitch and T. Tom  
Fulton and Keller  
Gowans, Corliff, et al.  
Gower, Tatum, et al.  
Green and Koppanyi  
Gruber  
Gruber and Beahrett  
Gruber and Friedman  
Gruber, Hazy and Gruber  
Gruber and Roberts  
Hirschfelder and Hazy  
Horowitz and Weale  
Horsley  
Irving, Bernson and Nelson  
Johanson  
Kreiser and Koser  
Koppanyi and Dille  
Koppanyi and Dille  
Lindemann  
Linger, Dille, Koppanyi  
Lorban  
Mason and Brand  
Nelson, Higgins, Spruth  
Nowak  
Oststead and Giragostotis  
Oststead and Giragostotis  
Patt  
Razbery and Haag  
Ross and Weaver  
Roth  
Severy, Essex, Mann  
Shonle  
Shonle et al.  
Shonle, Ketch, et al.  
Snyder  
Stenzon and Shonle  
Tabern and Stetberg  
Tabern and Volviter  
Ted  
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Adams  
Booker  
Bourne and Pauly  
Carnavy  
Delmonico  
Draper and Whitehead  
Elder and Harrison  
Elder and Hirsch  
Graber, Hairy & Graber  
Hietzman  
Lundy and Menzel  
Mark, Fox & Burstein  
Reynolds

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Bielzer  
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Esner  
J.A.M.A.  
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Tournaud and Joltrain  
Tournaud and Joltrain

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deBoda  
Eade  
Eddy and Erid  
Elek and Katz  
Hatcher and Weiss  
Haseilton and Koppay  
Haseilton, Oberst, et al  
Kath and Dumas  
Tamm and Seever  
U. S. Public Health Report

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Batterson & McCalland  
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Eliak and Schumann  
Everett  
Hardy Wolf & Goodell  
Lee  
Lickman  
New and Non-official Recipients  
Robbins  
Scott and Chen  
Scott, Kobbstadt & Chen  
Scott, Larrington & Jacoby  
Shidman & Johnson  
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Way

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## LOCAL ANESTHETICS

Adrian  
Barbier and Tavel

*South. M. J. Chemistry and Pharmacology*  
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Baier  
Baier and Hirschfelder  
Baylor and Harrison  
Booths  
Brenner and Tilden  
Cain and Rose  
Dunlop  
Eggleston and Hatcher  
Gasser and Erlanger  
Gilman, Goodman, et al.  
Graham and Peterson  
Hamel and Lamont  
Hill and MacDonald  
Hingston  
Mayer  
Potter and Whitacre  
Richards and Kuster  
Wastl

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Bagley  
Baldie, Herrick & Essex  
Bradshaw  
Bower, Clark, Wagoner & Burns  
Brook, Bell and Davidson  
Berch and Harrison  
Berch, Harrison & Blalock  
CoTel  
Davis  
Davis, et al.  
Dodd and Rovinsky  
Elliott  
Ezra  
Ferguson and North  
Gaak and Bone  
Gray and Parsons  
Harrison and Frank  
Hryman, Boeckert and Bert  
Hryman, Boeckert, Farber and Hiss  
Hill and MacDonald  
Isaac, et al.  
Koster, Shapiro, et al.  
Koster and Kussma  
Lahat  
Latterei and Leady  
Mason  
Robinson, Nussenz, and DuBois  
Schamberh  
Sever and Waters  
Shaw, Steele and Lamb  
Smith, Goldring and Chann  
Smith, Rovinsky, et al.  
Smith and Dexter  
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## CURARE AND CURARE-LIKE COMPOUNDS

Cole  
Cousse and Drippe  
Cullen and Gross  
Drippe and Ferguson  
Gill

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Griffith and Johnson  
Harbison, Beckert and Jialka  
Hewer et al.  
Oguzue, Paton, Zelnis  
Robbins and Landy  
Schallik  
Smith, Lotterri & Flickman  
Swanson, Henderson & Chen  
Whitacre and Fisher  
Wynsgarden, Triche and Stevens

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## ANALEPTIC DRUGS

Anderson  
Barlow  
Barlow  
Brazier Miles and Fiesinger  
Born  
Borsteln and Barrocinie  
Chen  
Dale  
Draper and Whitehead  
Dripps, Kirby and Johnson  
Eckinboff, Schmidt, et al.  
Eggleston  
Levy and Kirschbaum  
Fournier and Briere  
Henderson and Sparks  
Hildebrandt  
Jackson  
Klein  
Koppay, Lhargz and DDE  
Larkin  
Marshall, et al.  
Peschardt, Ramsay and Haag  
Raginsky  
Rosenfeld  
Rosa  
T. Linn and Kowlik  
Tatum and Werner  
Tusby and Essex  
Wood  
Wood

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## SYMPATHOMIMETIC DRUGS

Anderson  
Bry, Kates and Adriani  
Henderson  
Jung  
Metzler  
Morton and Tarniet  
Nikolschik & Wile  
Rosen and Adriani  
Scott and Chen  
Virt  
Yuker and Friden

*Anesthesiology*, 7 1, 1946. Methedrine  
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## INORGANIC GASES

Adrian  
Adrian and Batten  
Armstrong

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 Behnke  
 Behnke and Yarbrough  
 Bookman  
 Borford  
 Coryllos and Birnbaum  
 Eastman, Dunn and Krawickian  
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 Hell  
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## ANOXIA

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 Barack and Rosenzweig  
 Baxter White et al.  
 Bordick and Lee  
 Chase  
 Courville  
 Echols, O'Neil and Florens  
 Emerson and Van Lier  
 Hinrich
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## CARBON DIOXIDE ABSORPTION

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 Adriani and Rosenzweig  
 Brown  
 Goldstein and Dubois  
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 Rosenzweig  
 Severs, Stormont, Hathaway and Waters  
 Waters  
 Wiers  
 Waters
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## EXPLOSIONS

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 Cooper  
 Woodbridge Horton and Connell
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## PREMEDICATION

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 Carlson  
 Charvatin and Lusk  
 Connor  
 Herchenroth  
 Leigh and Britton  
 Phelps  
 Wangman and Hawk  
 Waters
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